IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

- - -

IN RE:	:	2:12-md-02342-CMR
	:	PHILADELPHIA, PA
ZOLOFT	:	
(SERTRALINE HYDROCHLORIDE)	:	September 2, 2015
PRODUCTS LIABILITY LITIGATION	:	

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TRANSCRIPT OF DAUBERT HEARING DAY 3
BEFORE THE HONORABLE CYNTHIA M. RUFE
UNITED STATES DISTRICT JUDGE

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I N D E X

Q. Let's go to -- doctor let me show you some testimony, see if it refreshes your recollection in Avandia.
A. Sure.
Q. See if we can do this.
MS. YATES: Your Honor, may I approach.
THE COURT: You may.
BY MS. YATES:
Q. Tiny print, I apologize. But this was your Avandia testimony, Judge Rufe in re Avandia. Okay. And so you're talking about, "We are fortunate because there are randomized controlled trials;" right?
A. Uh-huh.
Q. We talked about that, "And then subsequently then I would go on and look for information about the observational studies." Does that refresh your recollection? There are a number of observation studies?
A. There certainly were. I know -- memory there are certainly a number of observational studies about Avandia, but the body of my report and my testimony before Judge Rufe was about the, the randomized clinical trials.
Q. Oh, but you did review them; right?
A. I did review them, but I didn't put them in my report. I focused my report to use your words on the randomized clinical trial information for which there was a lot and there were a lot of -- there were close to 50 if my memory is

correct of randomized clinical trials. That was the focus of my report. That's my memory, I didn't spend any of my report discussing the observational study information. There certainly is some.

Q. Right. And so, okay. I'm not going to belabor it. All right. Let's go back to see if we can agree. You advised the Court and Avandia that there are formal techniques in a meta-analysis that are designed to make sure studies are weighted properly, you agree with that; right?

A. Yes. There's, meta-analysis is an averaging process as I indicated and it's going to weight it, different studies differently because of the, you know, for example the sample sizes can be substantially different.

Q. Because the little guys don't have the same weight as the big studies.

A. That's a nice way of putting it, yes.

Q. Okay. And these techniques make sure that you don't make the improper mistakes of averaging results so that no study has an undue influence; correct?

A. It should have its influence based on the weighting scheme which is usually a sample size driven scheme, but not always. Sometimes it's a little bit more sophisticated.

Q. And you've testify in this case that you can't do a meta-analysis because of this heterogeneity; correct?

A. I'm not saying you can't do it, you can it's just you

have to be very careful in interpreting it, because the averaging involved weighting or not can mislead you when you rely on the results of the summary when there's substantial variation in the individual trials.

Q. All right. Do you agree doctor that based on the heterogeneity the problem that you have in Zoloft is that the averaging that meta-analysis does pretty gets you nowhere, that's your opinion.

A. No. That's maybe, that's not my words. I wouldn't say get you nowhere. It's just you have to pay attention to the heterogeneity in interpreting the results that it gives. As I tried to make this clear yesterday if you have two studies one of which shows an odds ratio of two and one of which shows odds ratio of .5, let's say equally weighted to make it simple and you do a meta-analysis and you come out and report in the literature and an odds ratio of 1.0 and interpret no risk, first of all that's an incorrect statistical interpretation and it's clearly misleads, because of your women in the study had an odds ratio of 2. No one had an odds ratio of 1 as it happens, so that's why it's misleading and I can go on in greater detail as to why it's misleading, but I thought that made it clear that in those kinds of situations you can't resort to meta-analysis to resolve the inconsistency or the heterogeneity of the two studies.

Q. So, let's take a look at your deposition. Do you

remember having your deposition taken in a Zoloft case called Trace Foster it was pending in St. Louis?

A. I don't recall again, the details of the specific depositions.

Q. And we can put it up on the screen. If you turn to page 103, doctor, starting at line 7.

Q: You're perfectly capable of searching pub med [ph] and [indiscernible] defined set of inclusion, exclusion criteria and accumulating the data the same way Miles and the same way McDonough [ph] did; correct? And the answer goes on for a bit, so bear with me.

A: Well, but your misinterpreting my answer. That certainly was not the obstacle. The obstacle is the data itself does lend itself for a meta-analysis to be useful. A meta-analysis is an averaging process. If you want to take an apple and an orange and average it, there's no obstacle to doing it. You can do it. You can take orange juice and apple juice and mix them together. There's no physical obstacle to doing. Does it make sense? Sometimes averaging does. I've lived most of my life where average is terribly valuable, but the statisticians that have known for a long time that averaging can be horribly misleading and in this case with this amount of heterogeneity cross studies averaging gets you pretty much nowhere. So this is not a prime candidate of doing an effective meta-analysis in my view.

Q. Did I read that correctly?
A. You read that correctly and that's exactly what I said yesterday.
Q. Doctor, so you said there when you got this heterogeneity problem it's like mixing apples and oranges; right?
A. That would be the like the .5 and the 2 in my hypothetical example.
Q. Right. Do you recall that in Avandia you were asked about heterogeneity and whether it was like mixing apples and oranges?
A. I can't recall the details of the discussion 10 years ago.
Q. Isn't it true sir, that you told the Court that it's not like mixing apples and oranges, but rather mixing different types of apples?
A. Well, idea have to see the testimony.
Q. Okay.
A. It does sound like something I would say and that would refer -- the idea of apple and an orange is heterogeneity right? An apple's quite different. If I held it in my hand you could tell the difference; right?
Q. I sure hope so.
A. If I held two different varieties of an apple in my hand could you tell the difference?

Q. Possibly.
A. But maybe not; right.
Q. I could tell the difference in those wine glasses.
A. Yes, but that's an apple and an orange. Let's not change the metaphor. If I have two apples, distinct varieties of apples you probably couldn't, well maybe they look enough the same. Maybe I can combine these. That's exactly what I'm saying in this testimony here and that's exactly what I said yesterday, that's exactly what I'm saying now.

When you're doing an meta-analysis averaging it's fine in all other things being equal to do it when you have no heterogeneity, because then the averaging is voluble, you're not mixing a .5 and a 2 and coming out with this distorted in between value that no one experiences. And the value of meta-analysis as an Avandia is you get the increased precision that you get from combining multiple small studies.

So it's not that meta-analysis in itself is supposed to give you a magical different answer from the studies, that's not the purpose of meta-analysis. The purchase of meta-analysis if done correctly is to take homogeneous phenomenon each of which is imprecise average them and then you get a measure of the phenomenon you're interested in an odds ratio but with much more precision. That's the point of averaging always. That's the point of meta-analysis, but you don't do it and mislead people when they're so much

heterogeneity. That's what I said in this, you just read me, that's what I said back in the Avandia case. That's what I said yesterday and that's what I'm saying today.

Q. All right, doctor. Let's go to I believe it's the same transcript page 31. Oh, I'm sorry, it's not the same transcript. So we're now going to the Avandia transcript?

A. Okay.

Q. Okay? If you turn to page 31, line 6.

Q: Another thing I wanted to ask you --

A. Sorry, could you just -- which page was it?

Q. I am so sorry. Page 31.

A. 31, thank you.

Q. Line 6.

A. Thank you.

Q. And actually we can -- you'll see on the middle of page 30 yesterday the word heterogeneity came up; right? So, let's just give a little bit of context there. Now we can go to page 31 line 6.

Q: The other thing I wanted to ask you about is it like mixing apples and oranges?

A: Well, of course a key thing in a well conducted meta-analysis one of the limitations I think I refer to here is that the clinical trials that you are combining or observational studies if it's a meta-analysis of observational studies are not identical. They don't in fact one, you can

view that as a strength and a weakness. They are not at all identical population. They are not sampling from exactly the same population. The eligibility criteria for the trial that was designed for an efficacy reason may vary from trial to trial somewhat. They are done in different places. As I say, this is a weakness because you are now trying to mix things that were collected in different places. It's also a strength because as we heard yesterday one of the important issues in causation is seeing is a phenomena. Is there any idea of a risk replicated in different populations, because that is going to strengthen your belief that this is something causal but not peculiar to a particular trial or a particular population? So one of the limitations as I said and strength is you are mixing these things. It's not mixing apples and oranges, however, if I can use that analogy, it's mixing different varieties of apples. All of these studies have the same drugs applied to the treatment arm. They were all by in large with some notable exceptions studying diabetics. They were all essentially when the data was pulled out on adverse events they were all these investigators were honestly, I think trying to get at the same question. So this was not really trying to pull things from out of a hat and sort of jam them together, this was, most of these meta-analyses not all of them but most of them were well conducted, thoughtfully and trying to answer the question and summarize the information.

Q. Did I read that correctly?
A. I think you did.
Q. Thank you. Now doctor, I think we're well aware of your criticisms of the meta-analyses on Zoloft, but you did a mini meta-analysis; right?
A. I did as I described yesterday in the paused analysis we had two major studies that allowed you to independently look at the question of comparing woman on Zoloft and comparing those who continued to use Zoloft during the first trimester by some definition versus those who didn't and I combined those two in front of the Court yesterday.
Q. Right. So there's a couple of steps here. Let's see if we can go one at that time. You performed a calculation or a reanalysis of some of the Huybrechts data comparing what you say women have filled the prescription in the first trimester and women who did not fill a prescription in the first trimester; right?
A. One or more prescriptions filled, yes.
Q. Okay. And this analysis or calculation is not part of the peer review published study of Huybrechts; right?
A. Well, the data are there in the peer review publication. That particular calculation is not.
Q. Right. That was my question. And it's not part of the investigator's methods; correct?
A. I don't know if it's -- but an investigator certainly

deliberately tried to separate out these women that had at least one prescription filled during pregnancy, because I believe in their sensitivity analysis they believe that was a more rock-hard measure of exposure if you actually fill a prescription you're not only were exposed in that you had a previous prescription that took you through the first days after conception but then you also filled one. From their sensitivity analysis perception they thought that was a more definitive measure of exposure and that's what they used it for and I used the same data but in a slightly different way.

Q. Sir, your calculation was not part of the investigator's methods set forth in the peer review published article?

A. As I just indicated, yes, the data was there in the supplement, but not that particular calculation, that is new, yes.

Q. And in fact, Dr. Huybrechts has referred to your reanalysis as post hoc subgroup analysis; correct?

A. As well as referencing it as interesting.

Q. And after the fact sub -- post hoc took a little bit of Latin means after the fact; right?

A. I actually took a little bit more Latin than you.

Q. There you go.

A. But I'm surprised you didn't.

Q. I rejected it. I looked at it and rejected it. You

haven't published your reanalysis, sir?
A. No, I've asked, as I indicated yesterday I believe to take the data from someone else's paper without approaching that author directly and asking them to collaborate would be not in my scientific approach, so I have asked the author if she would be willing to publish them with me, because she -- it's her data and she knows that data and I think that would be the right way. And as we discussed yesterday we're on route somewhere. I don't know how it will play out in the end. She may not wish to be involved given how much contact she's had from lawyers in this case.
Q. She politely declined; right?
A. No. At the last e-mail she actually indicated that she would maybe see if some of team could help.
Q. Let me back up. When you asked her to be a co-author that e-mail politely declined; correct?
A. Yes, she said she had too many other projects at that point if you want to look at the e-mails, please do.
Q. And --
A. And then at the last e-mail when he had worked through what I was getting a she said that's an interesting possibility or something and then I'll see if -- I'll bring it up to my team and see if someone else can. I assume she's too busy.
Q. That was your request for the data?

A. No. That was the request to publish the data -- well, that was my request for them to run the analysis adjusting for --

Q. Right.

A. -- confounding. I assumed if they did that they would be willing to stand behind their work and go publish, but I can't --

Q. That wasn't the question was it doctor?

A. I can't -- if you could just let me finish. I couldn't, I can't speak to that. We're in the middle of something here. I wrote to Dr. Huybrechts saying here is an interesting analysis it's your data would you co-author? She said I'm too busy and any way it doesn't adjust for confounding. I said, exactly, that's why I need your help and would you be -- I need the raw data. She said, I'm too busy I'll see if my team can help.

Now whether that leads to a publication that they want to be associated with or not that's for the future to decide.

Q. You have no idea right now; right?

A. Whether it will be done? Well, I can't do it. I have no control, I think is a better way of putting it.

Q. Right.

A. Yes.

Q. And the data you extracted was from the supplement from the Huybrechts study; right?

A. That's right. The online supplement.
Q. And you defined some users in that supplement as paused.
A. Well, I put paused in quotes, because --
Q. So did I.
A. Yes -- and so did you -- because the word pause comes from the Jimenez-Solem paper and --
Q. I'm coming to that, I promise.
A. I understand. I --
Q. I'm just trying to do this -- right now the questions are this long and the answers are really long doctor and I really would appreciate it if you could focus a little bit more on my question. I will get there and then your counsel has a chance to do a redirect.
A. I'm sorry, I'm a teacher I can't help it. I can't turn it off. That's why I put the word paused in quotes. It's a slightly different definition than what's used in Jimenez-Solem where they used the word pause.
Q. Precisely. So, number one, Dr. Huybrechts did not define this population as paused; correct?
A. She didn't use that word, that is correct.
Q. And number two, your definition of paused is different from the Jimenez-Solem definition; right?
A. Yes. As I just indicated, yes.
Q. And as you said, Dr. Huybrechts pointed out you haven't

adjusted for compounding; corrects?
A. And we discussed that yesterday and the rest of the story.
Q. Now, doctor, yesterday there were a couple of slides, pie charts and I'm sorry, I only have black and white, but if I can use the Elmo [ph] maybe that's easier [indiscernible]. This pie chart was shown of this is your reanalysis of the Huybrechts data and I apologize that's my handwriting, Jewell's definition of pause, we've already gone through that. And you've an odds ratio of 1.87 confidence in yours was 1.07 to 2.39 P value of .02; right? That's what you showed us yesterday?
A. Yes. I showed two of these I believe and this is the one to be precise that refers to the "paused group" I mean the exposed as filling one or more prescriptions.
Q. Right. There was another one that talked about after Dr. Gibbons commented you went and did two or more; right?
A. Correct.
Q. But then we saw another slide meta-analysis Huybrechts and Jimenez-Solem. Huybrechts [indiscernible] odds ratio 1.9 confidences of 1.1 to 3.3.
A. Could you show me the previous slide just so I can --
Q. Yes.
A. Because that's where I think you're going. Yes, that doesn't look right.

Q. It doesn't right does it doctor?
A. Yes, that's -- one of those is --
Q. Do we know which one is wrong?
A. Well it might take me a minute. Because if I can take logs I could do the symmetry. Maybe Dr. Kimmel can do it for me, he's better at that with his eye. I can't -- with that, I think to be fair I should correct one of those slides after I've had a chance to be in a dark room for two minutes.
Q. Okay. All right. One of them is wrong we don't know which one?
A. Yes. The upper bound there looks incorrect on one of those.
Q. Okay. And just so we're clear based on your communications with Dr. Huybrechts you did not mean your unpublished reanalysis to supersede Dr. Huybrechts' big published study; right?
A. No. And I told her that, of course I didn't intend that.
Q. Right. When you did your meta-analysis do you know if you used the correct numbers?
A. Which meta-analysis?
Q. So you --
A. Oh, you mean the two studies?
Q. Yes.
A. I would've used the raw data itself, not the summary

results. So I did it myself using the raw data, not, so it's the transcription error in one of those upper bounds.

Q. All right.

MS. YATES: Your Honor, I'm about to move on and I can hopefully tighten things up. I'm happy to go on or I'm not sure.

THE COURT: Well, it is a lunch break time.

MS. YATES: Lunch break. Okay.

THE COURT: And I think we ask take the hour again if that's not enough let me know, because we can easily come back at 2:00, but it is appropriate to break now for a lurch recess. So why don't we get here in an hour and assess where we are and that would be 10 minutes to 2:00.

MS. YATES: Thank you, Your Honor.

THE COURT: Thank you.

(Whereupon there was a recess in the proceeding from 12:49 p.m. to 1:56 p.m.)

THE COURT: Have a seat.

BY MS. YATES:

Q. Hello doctor.

A. High.

Q. We left off with your post hoc subgroup analysis from the Huybrechts that you then created your mini meta-analysis with Jimenez-Solem and we were agreeing that that subgroup reanalysis does not replace the overall study results, so I

just wanted to go to Dr. Huybrechts conclusion based on her overall study results if we could show that please. Huybrechts page 2405. Huybrechts is in your binder and we'll try and bring it up here as well, but page 2405. Okay? With me doctor?

A. Not yet.

Q. Lower right-hand side, right-hand column, page 2405.

A. Yes, I'm with you now.

Q. All right. The authors in Huybrechts conclude, in conclusion our results suggest that the use of antidepressants during the first trimester does not substantively increase the risk of specific cardiac defects. Did I read that correctly?

A. You read it correctly.

Q. And then they go onto state if you turn onto page 2405 to 2406. The accumulated evidence. The accumulated evidence implies low absolute risks and argues against important teratogenic effects associated with the most commonly used antidepressant medications. Did I read that correctly?

A. You did.

Q. And there published peer review methodology led them to these conclusions; correct?

A. Their main analysis led to their conclusions, yes.

Q. And their main analysis was the published peer reviewed analysis; correct?

A. Correct. And that's the analysis that you agreed my

paused analysis does not supplant or supersede in any way. It add to it rather than supersedes it in my view.

Q. Understood. Doctor, I wanted to move on. Several places in your report you refer to the word trend; correct?

A. Probably, yes, it's a word I use a bit.

Q. All right. And you use -- for example on page 4 of your report so that's tab 176. Page 4 of your report you refer to a trend when you're discussing nonsignificant findings that you say in support increased risk; right? Let's just take a look. No, that's not it. Page 4, nonsignificant -- I think we're all having trouble reading what we've got on our screens, Your Honor. I know I am.

THE COURT: Do you have -- Dr. Jewell's report in binder that he has handy.

MS. YATES: You know what, I believe it's in -- good point. Thank you, Your Honor. It's in the binder from yesterday I believe. Tab A from Mr. Zonies' binder.

THE WITNESS: I have it.

MS. YATES: You have it?

THE WITNESS: Yes.

MS. YATES: Tab 1, I'm sorry.

THE COURT: Tab 1.

MS. YATES: So if we go and it's now on the screen I'm being told. Okay. I can't read that. So, somebody's going to have to help me on that.

BY MS. YATES:
Q. You discussed, you used the word trend. We're looking at page 4 of your report and you refer to result that reflect statistically significant increased risk and nonsignificant supporting trends in risks (positive associations); right? That's one place where you use it in your report?
A. Yes. So, there I'm using it to say a positive association, that's where I'm using the word, but it's not statistically significant.
Q. Right. And you also use it when you discuss dose response if we go to page 60 of your report you reference trends in discussing an increased risk with dose with increased risks; right?
A. Yes, the word is there being used a little bit differently because it's in the context of a dose response where a trend has its own meaning --
Q. Right.
A. -- that the risk goes up or down monotonically. And, but again I'm using it there to point out that the evidence from Huybrechts and Jimenez-Solem regarding dose response is not statistically significant.
Q. Okay. You agree, sir, that there's no generally accepted definition within the profession of biostatistics for the word trend?
A. Not for the English word, no. I mean, I think it can

mean different things in different context as we just saw.
Q. Okay. And there's no textbook that defines trending data; correct?
A. I would be shocked if there was.
Q. All right.
A. It's here being really used to point out the lack of statistical significance, but yet a positive association.
Q. Okay. In fact trend is not a word you really like to use is it doctor?
A. Why, I just said I kind of like the word, but you have to give me a context. I guess there might be somewhere where I don't like to I'm sure --
Q. All right.
A. -- I've said in the past in another context that I don't like the word trend for a specific situation.
Q. Well, it looks like in Avandia you didn't like the word trend?
A. Possibly. I would have to see the --
Q. Shall we look?
A. Sure. I would have to see the context.
Q. Okay. Let's -- you have the Avandia transcript, I believe?
A. I do.
Q. Let's go to page 75 and turning over to 76, so it's right at the end of 75 line 24 going over to page 76 line 14.

A. Seven, I'm sorry, 75, 76?
Q. Yes, 75, line 24.
A. Okay.
Q: There was some testimony about trends and then I believe there was actually a question from the bench about trends. I want to know is there textbook that defines trending data.
A: No. I mean, as I said, I don't like that word. I don't use it much, my -- I don't use it myself very much. It's really kind of a loosely used word to say when you want summarize a set of trials and say do they tend to have a tendency to give a certain picture or not. Does it tend to be a little bit red or a little bit blue? And so the trend there is very informal, just saying do these trials have a tendency or a trend towards being negative or positive with regard to a comparison. That is the only way I've seen that word used. It's not a word I use a lot myself.
Q. Did I read that correctly?
A. You read it correctly.
Q. Okay. Now, as part of your use of the word trend as you said, you use that when you have nonstatistically significant findings?
A. Yes, so that's a different context from the text you just read from Avandia where it's not talking about that situation.

Q. Right.
A. But if you want me to explain that I'm happy to do so.
Q. But my question that actually related to that was you said you didn't like the word trend.
A. In that context and the context is described a little bit there, but I could go into more detail, but it's different from the way it's been used in that I -- the other two examples you just gave.
Q. It depends on the situation?
A. Well, English words do tend to depend on the context you're using them, yes.
Q. All right. But in Zoloft you use it for nonstatistically significant findings; right?
A. In the dose response, yes. I use it in that context to refer to non-significance?
Q. Let's separate out dose response for a doctor. Let's focus on the nonstatistically findings, because you cite several studies that "support" your trend; right? Support a trend in increased risk?
A. Uh-huh.
Q. Yes? So let's start with Alwan 2007. You cite Alwan and we can go to your report at pages 4 to 5. You support Alwan finding a 1.3 odds ratio for conotruncal heart defects as "support for an increased risk" correct?
A. I'm sorry, I'm not with where you are. You said 4 to

5.

Q. Okay.

A. But I didn't get there quick enough.

Q. I'm sorry. I will wait.

A. Whereabouts on 4?

THE COURT: Your report.

THE WITNESS: Yes, I'm in my report on 4 and 5, but I'm just not sure where you're reading from.

BY MS. YATES:

Q. Okay. Let's see if we can help you. All right. So you say in your report page 4, the results that reflects statistically significant increased risk and nonsignificant supporting trend in risk positive associations for exposure specifically to Zoloft include turn the page and you've got a list of studies and their findings; right?

A. Yes, that list is as I indicated the list of all nonstatistically significant results but which it indicated increased in risk and that's the definition of that list.

Q. Right. And --

A. And Alwan is one of them.

Q. Alwan 2007 you have as showing supporting your trend in increased risk, but let's go to Alwan, page 2684 and let's take a look at the author's conclusion.

A. Okay.

Q. All right. So, here we have Dr. Jewell taken your

language from your report and we're going to go and look at what the Alwan 2007 authors conclude; okay?

A. Yes, and we're on what page on Alwan?

Q. 2684.

A. Thank you.

Q. And they conclude maternal use of SSRIs during pregnancy was not associated with significantly increased risks of congenital heart defects or of most other categories of birth defects; did I read that correctly?

A. Yes.

Q. And there peer review published methodology led them to that conclusion; correct?

A. I assume.

Q. And you disagree with that conclusion?

A. Well, first of all they're talking about somewhat different things, so on the left I'm talk -- which you haven't noted on the slide, on the left I'm talking about Zoloft and cardiac defects and in this case --

Q. Right.

A. -- you picked out the one which is conotruncal subcategory of all cardiac. On the right-hand side the authors are talking about their overall conclusion that --

Q. Right.

A. -- it is all SSRIs and I guess they're talking about all cardiac --

Q. Right.
A. -- heart defects.
Q. So --
A. But you didn't put on the left-hand was the Alwan result for Zoloft for all cardiac which is not in the list you just put up.
Q. I'm going just with your report, right. So different lists. Stick with me, I'm on that one --
A. Yes, but you're just comparing here two statements about two different things that's all I'm pointing out.
Q. And I'm going to clear that up doctor.
A. Great.
Q. I went to your report, your list of nonstatistically significant findings; right?
A. Correct.
Q. Now we know that the authors of each and every study doesn't make a concluding statement about every single finding; right?
A. Correct.
Q. That would be an awfully long study. So what we did was she just showed a result that was nonstatistically significant; correct?
A. Correct.
Q. And all I'm trying to do is show the overall conclusion, because you picked out various results from Alwan;

right?
A. No. I reported all of the results from Alwan that are due to Zoloft and elsewhere in my report I give the number for Alwan for all congenital heart defects that corresponds to their conclusion on the right. Albeit theirs is for all SSRIs.
Q. Okay.
A. So, we should probably go to my report if you want to compare them and look at where did Alwan appear.
Q. Sure. All right. Let's look at that then doctor and go to page 2691 table 3. You with me?
A. Yes, I'm with you in the Alwan paper.
Q. Okay.
A. Yes.
Q. Yes. Page 2691, table 3.
A. Yes.
Q. All right. Cardiac birth defects?
A. Yes.
Q. For -- go to Sertraline which is Zoloft, number of exposed 22. Odds ratio, adjusted odds ratio 0.7 confidence intervals 0.4 to 1.3; did I read that correctly?
A. You did.
Q. Okay.
A. Now that result is reported on page 12 as a result that does not have a supporting trend to my opinion specifically.

So, that's why you cannot put those two sentences on the same page, because where I do talk about the result that Alwan is discussing, I have it in the right place in my report. It's less than one, it does not provide a supporting trend, it's quite explicitly clear on my report.

Q. I was coming to that. That's fine, I -- we went straight to it, that fine. Let me see if I can move this along, doctor. But if we go back to page -- just so we're clear, if we go back to that list in your report, they are the nonstatistically significant findings and you cite in addition to Alwan you cite Kalen [ph], Maum [ph], and Luick [ph] because they had some non-statistical findings, Colvin, I mean there are multiple studies in other words and I just want to be clear they're nonstatistically significant that fits into your trend bucket.

A. This is the definition of this list is the list of all the results in those core studies that show an increase in risk, but, one that is not statistically significant for that specific comparison.

Q. Understood.

MS. YATES: May I have a moment, Your Honor because I may have just short-cutted something.

THE COURT: Sure.

BY MS. YATES:

Q. All right. Let's move to -- I'm going to come back to

that, I apologize, Your Honor. I'm trying to get organized and apparently I'm not doing a very good job. Well let's go to -- you're familiar with Maum 2011; right?

A. That is, yes, one of the studies.

Q. And we can again pull up your report page 4 to 5 doctor, if you have it?

A. I have it.

Q. You cite two nonsignificant findings from Maum as part of your supporting trend in risk; is that right?

A. They are two positive associations there that are not statistically significant; correct.

Q. Right. And that's conotruncal and --

A. Yes.

Q. -- transposition of the great arteries or TGA; is that correct?

A. That is correct.

Q. And you recently testified in trial that the findings in Maum for TGA is evidence that supports the claim that Zoloft causes TGA; correct?

A. Well, that in the context of a lot longer discussion, because for TGA specifically that's the only finding reported in any of the studies we've discussed yesterday and today, it's based on very few TGA cases, so this comes back to the grouping discussion that when you go down to subgroups as rare as TGAs you cannot possibly rely on that one single study in

isolation to prove causation. You can only rely on the fact that it's contained in the larger group of all cardiac defects where there is evidently an association.

Q. Sir, am I correct that you testified to a jury in Philadelphia that based on that one reported case of TGA in the Maum study that Zoloft causes TGA?

A. And that's the reason I just described, because as I've already testified at deposition and was discussed at trial that Maum finding is the only one reported for TGA. There are very few TGA cases even in the Maum study that reports it. If you only had that information in isolation you could not really come to a conclusion of causation it's too much variability, there's just -- you can see from the length of the confidence interval there for TGA it stretches from .35 to 18.62 so there's just really very little precision, almost none. So you have to fall back on the argument that we discussed yesterday which is what I tried to explain to the jury which is when you come to such a rare subcategory you have to rely on its membership of a larger group where you have established association.

Q. So, you've testified in that trial -- the birth defect was TGA; right?

A. I think there was multiple birth defects, I was -- I think I testified that I wasn't really that conscious of the specific nature of the birth defects by that particular child,

suffered by particular child.
Q. Okay. And Maum to your recollection was the only study that reported on the breakout that they actually reported on TGA?
A. Yes, amongst those core studies in my report.
Q. Okay. And within Maum it was one case; right? One reported case?
A. One exposed case, I believe.
Q. One exposed case; right? Okay.
A. There had to be some unexposed cased to gate an odds ratio calculation that's as described.
Q. By women who didn't take Zoloft had children with TGA?
A. Yes, there were a huge number, more of them of course is so there must have been at least one or two in there also, but it's rare.
Q. And the Maum authors don't refer to this nonstatistically significant finding in their conclusion as one of the increased risk they found do they?
A. No, I don't remember, but I wouldn't be surprised if they didn't because of the width of that confidence interval as I described there's really in isolation there's no real information. They reported it, but I would doubt they would point it out in their conclusion section.
Q. Okay. They didn't point it out as a significant finding; right? Because it wasn't statistically significant;

correct?
A. It's absolutely not statistically significant, yes.
Q. Okay. Doctor, the Colvin 2011 study that didn't adjust, that didn't do any adjustment on the results did it?
A. You mean in terms of confounding?
Q. Right.
A. I'd have to go back and look at the paper, not all the early papers were able to or did adjust for confounding, but I don't recall specifically the details without going back and looking.
Q. Okay. I can refresh your recollection with some testimony.
A. Sure.
Q. Okay. Let's -- Prozac deposition. Doctor, I believe this was a deposition taken in the Prozac case.
A. Thank you.
Q. If you would turn, sir, to page 170.
A. Page 170, yes.
Q. Line 14.
A. Yes.
Q. Okay. And --
Q: So, which of the 8 studies that did adjustments?
A: Well now, I said before the break and relying on memory so I would have to go back to each of them, but I

believe Alwan and Luick [ph] both did adjustment, I'm having a hard time this is not the right place to look at this.

Mr. Zonies: Your report [indiscernible] the witness is it in my report.

A: What page are you looking at?

Mr. Zonies: Page 14.

Q. Scroll down.

A: I knew I got it somewhere, but I just don't remember these (reviewing document). Yes, the chart in my report gives a -- this is what I did. So, you were talking about sensitivity analysis. So there is the -- there were actually not 8 in there, but Colvin I wasn't sure. I now believe since I wrote the report that the fact that the study adjusted odds ratio -- that the study adjusted odds ratio and the odds ratio that Lilly used are identical and having reread Colvin a number of times I don't believe they made any adjustments. So you can ignore the Colvin on the chart on the page 14, but the other 7 clearly there are 7 of them that did Maum, Dealsitrin [ph], Cornum, Reese Kalen, Petersen Alwan and Lloyd.

Q. Did I read that correctly?

A. You did.

Q. Does that refresh recollection, sir, that Colvin did not adjust for confounding?

A. Yes. This is in terms of Prozac, but I assume the same

answer is true for Zoloft, they didn't do an adjustment for confounding. If you actually turn to page 105 of the same deposition which I'm sure you've read the whole thing, it says on line 11 if I can read out, "and that's just" -- I'm talking about misclassification, and then so, that's one of the issues that's there, confounding by other factors is an issue for some other studies, because we only have unadjusted results, I don't throw those out either. I don't throw any of the studies out as it happens. So there I'm pointing out that there are some of the studies where only unadjusted results are provided and that's all I have.

Q. Right. And my next question was going to be that's in relation to Prozac, but you assume that that's also true for the data on Zoloft. We have no reason to disagree with that?

A. Sitting here today I would assume that, yes.

Q. So, if your forest plot only includes studies that were adjusted for confounding Colvin should not be on there; right?

A. Well, I think I was trying to put on the visualization all of the results that were there, unadjusted or not, but every time there was an adjustment I wanted to put in the adjusted result.

Q. Right.

A. That's what I believe that visualization tells us.

Q. Okay. So if you had said that the forest plot only contained adjusted findings that would be wrong?

A. For Colvin it would be wrong, yes, because we've just determined it's one of the few if maybe the only that has completely unadjusted results according to what you just read to me.

Q. Okay. All right. Doctor, we mentioned the word trend in relation to dose response and if we turn to page 60 of your report tab 110 you have a section entitled dose response; right?

A. I do, it's one of the Bradford Hill criteria.

Q. Right. And you write the epidemiological evidence, can you find that for me?

A. At the bottom maybe?

Q. Yes, it's on the epidemiological evidence. In some, the epidemiological evidence with regard to dose response for Zoloft and cardiovascular malformations specifically is limited, however, the evidence that does exist shows a trend towards an increasing risk with increased dosing. Did I read that correctly?

A. You read that correctly.

Q. And the two studies you rely on if we go to, if we look at those citations 131 and 132 are actually Jimenez-Solem and Huybrechts; correct?

A. That is correct.

Q. All right. Well, let's look at what the scientists who conducted the Jimenez-Solem study and the Huybrechts study

concluded about whether their studies found a dose response relationship. Let's first go to Jimenez-Solem at page 5, I think you have that doctor.

A. Jimenez-Solem, okay. Page --

Q. Five.

A. Five, okay. I'm there.

Q. Right. The author states analyzing the effect. Apparently my tech person can't read my mind. I don't know why you don't know exactly where I am, Roger. Okay. Are you with me doctor?

A. I see where you're starting to read from, yes.

Q. All right. Jimenez-Solem the authors state, analyzing the effective dose is a continuous variable yielded no dose response association. Did I read that correctly?

A. You did.

Q. And if we go to page 8 of Jimenez-Solem.

A. Yes.

Q. The authors state their conclusion regarding confounding by indication are sustained by the lack of relationship between dose and risk. Did I read that correctly?

A. I said that, yes.

Q. All right. Let's move to Huybrechts.

A. If I can just stop for a second, because I want to correct what you did and make it clear that everyone

understands the first paragraph you read from Jimenez-Solem was not about Zoloft it was not about cardiac defects it was about all malformations if I understand it correct late. And though it says a sentence for individual major malformations we found similar associations, but the two quoted odds ratios are for major malformations and they actually are contradictory to the dose response, they go down slightly though it's statistically indistinguishable.

So, there's no question there that when you look at my report you get the two odds ratios for low and high dose in Jimenez-Solem which you didn't read which is 1.8 for the low dose, odds ratio for Zoloft now specifically and specifically for cardiac and for high dose it's 2.3.

Now, if we've learned anything in these last two days, we should know by now you can't tell the difference statistically with this level of data between 1.8 and 2.3, so it's not statistically significant, but it is an increase response as you increase the dose as reported specific in Jimenez-Solem for those. It's just not statistically significant. I have no disagreement there at all.

Q. Okay. And they don't refer to it in their overall statement where they're talking bigger than just the cardiac this was sustained by the lack of relationship between dose and risk; correct doctor?

A. Well, we've already talking about their conclusion and

since they're not starting from the conclusion that there is a risk then it's hard to see how dose response would confirm with conclusion of no risk or no increased risk, so that doesn't surprise me they said that. The bottom line is as I say in my report and as all the authors agree on the data on dose response in the human studies is really extremely limited and even the definition of high and low dose as reported by the experts differs enormously between Jimenez-Solem and the one you're just going to Huybrechts.

Q. Okay. Well, let's go to Huybrechts. Let's go to Huybrechts page 2402.

A. I'm there.

Q. Okay. Huybrechts page 2402, we did not observe a dose response relationship either with respect to the first dose or with respect to the highest dose dispensed. Did I read that correctly?

A. You read it correctly on the screen. I'm just trying to locate -- oh, yes, I'm with you. Yes, you read it correctly.

Q. Okay. All right. And then they have in parentheses table S17 in the supplementary appendix; right?

A. They do refer to table S17.

Q. Okay.

A. And as again this is the same issue that arose with Jimenez-Solem table S17 which is on page 31 has a number of

results including Paroxetine, Zoloft, Fluoxetine, TCAs, SNRIs and so on. So, they're making a blanket statement there. In my own report I only pulled out the Zoloft specific information and specific for cardiac the odds ratio for low dose according to Huybrechts associated with Zoloft as 1.1. For what she refers to as medium dose it's 1.33, of course again, there's no way that's going to be statistically significant and no one claims it is and that's all it is, it's just an association in the direction of a dose response that is not statistically significant nor would you expect it to be with this size of data set.

Q. Understood. Doctor we've talked about a lot of studies and despite my efforts to try and say that I don't need to talk about anymore, my team seems to think I need to talk about some more, but it's going to be focused on the issue of confound ing by indication which I know we've discussed a little bit. But you agree that confounding by indication is a particular concern in studies of depressed women; right?

A. It's a concern in all observational studies where the outcome is a clinical condition, yes.

Q. Right.

A. Or is it -- sorry, let me rephrase that. When the outcome is in a group of women or a group of individuals with a clinical condition.

Q. Excuse me, sorry. And there are different methods by

which investigators can attempt to minimize confounding by indication; correct?

A. Correct.

Q. And that's true in several of the more recent studies that we've seen in Zoloft that they -- as size progress the later studies attempt today employ these methods that were not used in earlier studies; fair?

A. I think the, yes, the thing your referring to most prominently is the thing we discussed yesterday which is to use only depressed women with a diagnosis of depression for all of the pregnancies those exposed to Zoloft or an SSRI or those not exposed where prior studies in this chart often had used all women in there and then worried that in fact it might be that that was not comparing an effective comparison group.

Q. Right. And so let's go through some of the methods that these scientists used to attempt to examine confounding by indication. So, Jimenez-Solem 2012 attempted a new method of examining confounding by indication by comparing SSRI users to women who paused their use during pregnancy; right?

A. That was the way they tackled the issue; correct.

Q. Right. And in fact they commented on the prior studies that the data was conflicting and that some of these and none of them hadn't successfully managed to differentiate between the consequences of the drugs themselves and the underlying disease; right?

A. That was the concern, yes and it's been a consistent concern throughout this literature.
Q. And Jimenez-Solem they did the nationwide study in Denmark; right?
A. Correct.
Q. And they focused on congenital heart defects in comparing this paused group to look at, to account for special characteristics of women using antidepressants?
A. Correct.
Q. All right. And you agree, sir, that that's a step forward in science; right?
A. I think attempts to adjust for bias or control for bias are always a step forward, yes.
Q. Let's look at another one. Ban [ph] 2014, right? I know I --
A. I didn't know what the question was, sorry.
Q. Sorry. Ban was in 2014, wasn't it doctor?
A. Okay.
Q. If I get specific I'm sort of going to do what I just did with Jimenez-Solem but if we need to go to the actual study we can do that?
A. Oh, you don't need it, okay. Well, then I take your word for it that it was 2014. It sounds right to me.
Q. Okay. Ban control for depression by comparing women with depression who are taking SSRIs and to those who are

depressed who are not taking medicines; right?
A. I'd have to go back to the paper, but that sounds familiar.
Q. Does that sound right?
A. But if we want to be exact we should look at the paper.
Q. All right. Can we find that quickly?
A. Sure.
Q. Sure. Who said sure?
A. I'm getting good at it now. I have it.
Q. You have it?
A. I do.
Q. Excellent.
A. And you're absolutely right. It is 2014.
Q. There you go. And just to confirm they, the study control for depression by comparing women with depression who were taking SSRIs and those with depression who were unmedicated; right?
A. Well, that I would have to get into the text a little bit to confirm my memory.
Q. Right.
A. Do you want me to do that or wait?
Q. I would like you to either take my word or confirm.
A. I'm happy to take your word at this point, because I'm sure someone will point out if you're wrong.
Q. I'm sure they will. Doctor can key agree that this Ban

is the first study to do that type of depression restricted comparison certainly when we're talking about Zoloft and the SSRIs?

A. Again, without having to look at all the studies, I'm perfectly willing to take your word, that was the first of the 10 to a dozen or so studies that started to use that approach.

Q. Okay. And this is another study that you cite of evidence of an increased risk between Zoloft and cardiac birth defects, right? Page 24 of your report.

A. Okay. This is for the all cardiac, it's a nonsignificant positive association; that is correct.

Q. Okay. And if we apply their depression restricted comparison and look at their conclusion, so if you go to Ban page 1, abstract conclusions, are you with me doctor?

A. Yes. Well, I'm not where -- if you tell me a page number it helps.

Q. Sorry, it is the front page, page 1?

A. Okay.

Q. They're conclusion, overall MCA, and that's major congenital anomaly, again, that's bigger than cardiac and subcategories; right?

A. It is.

Q. Risk did not increase with maternal depression or with antidepressant prescriptions. Paroxetine was associated with increases of heart anomalies although this could represent a

chance finding from a large number of comparison under, comparisons under taken. Did I read that correctly?

A. You did.

Q. So based on their depression restricted methodology that they employed to help counter this confounding problem for cardiac, for heart anomalies they found no increased risk accept Paroxetine which is Paxil; correct?

A. Yes, I think they're pulling out the significant result then. We've had a lot of discussion that in an individual study they're not going to, in isolation, they're not going to report an increased risk of what was it 39 percent unless its significant and they didn't and that would be consistent with what we discussed this morning in the New England journal for example.

Q. All right. Let's turn to very quickly again, just on the issue of confounding, Huybrechts 2014 done by Harvard Medical School; right?

A. Brigham and Young I think at Harvard.

Q. At Harvard, yes. Largest study of SSRIs and Zoloft to date. Nearly a million women.

A. I can't remember Furu.

Q. Furu was 2.3 million?

A. Furu I think had more women, yes.

Q. Okay. So, this one would be the largest U.S.?

A. It's certainly the largest U.S., yes.

Q. Okay. Over 14,000 women exposed to Zoloft?
A. Gen, I can't remember these numbers, but if you have them there or I can take your word for it, but.
Q. Okay. If I say anything that you want to verify doctor or troubles you will stop and look at the study, okay? But it's 2, page 2,402, table 2?
A. Yes, just the way I work is I tend to like to look at the original information.
Q. That's fine. So there we have it, table 2, Sertraline, 14,000 women.
A. Yes, I see that now, thank you.
Q. All right. So, similar to the Ban study one step of the analysis that was performed by the investigators of the Huybrechts study was to do an adjustment made just for depression; right?
A. Yes, they originally had more pregnancies, more mothers in their data set then depressed mothers and then they subsequently restricted the comparison group and actually the Zoloft exposed group because not everyone taking Zoloft has a diagnosis of depression. They restricted the comparison to just those mothers with a diagnosis of depression.
Q. Right, so they had a depression restricted analysis comparing depressed women who took Zoloft and depressed women who were unmedicated?
A. Yes, were depressed means a diagnosis of depression.

Q. Right.
A. Cause it's --
Q. And limiting the results to that analysis of the depression restricted cohort is yielded a nonsignificant odds ratio. Well, let's turn to it. Page 2403 figure 1, doctor. Sorry, I didn't want to get ahead of you.
A. That's okay. Figure 1, yes.
Q. Okay. So, when you limit the results to the analysis of the depression restricted cohort it yielded a nonsignificant odds ratio of 1.16 confidence intervals .95 to 1.41 and that's for Zoloft and cardiac defects; correct?
A. That's correct. And that's a change from the unadjusted the full analysis which of course used a lot more women which was 1.24. That happened to be statistically significant, I didn't report it as that in my report because I wanted to use --
Q. The adjusted.
A. -- the most extreme form of adjustment that the authors reported. But that effect of restricting to the women who had a diagnoses of depression in both exposed and unexposed groups changed the odds ratio from one, for Sertraline from 1.27 if I am looking correctly to 1.16, so roughly a 10 percent drop in the odds ratio. So that gives you a sense which is I think helpful in a courtroom or helpful in lay readers, that gives you a sense of how big an impact would it be to do that kind

of adjustment for confounding by indication. If we would go back to Colvin now, who you said or some of the earlier ones who you said didn't do that adjustment because they didn't have the data or dint think of the idea that way, I have not put this in my report, but then you can think well, what would've been the impact, this is the way a statistician thinks. What would've been the impact if Colvin had done that?

Well, the best evidence we have is it will do something like it did in Huybrechts. It will change it by 10 percent. That's what I comment in my report that the effect of confounding by indication when you do this particular solution is important but not enormous and dramatic, it changes the odds ratio by 10 percent, 9 percent, I need to be exact.

Q. And that depression restricted analysis, that's not the end of the Huybrechts analysis; right? They also performed a propensity score?

A. Yes, but that propensity score now has less to do with confounding by indication and more to do with general confounding by other facts as we discussed yesterday.

Q. Okay. So, first step and then they did the second step which was more to do with less specific confounding concerns?

A. Other variables other than diagnosis of depression, yes.

Q. All right.

A. Obesity, maternal age, things like that.
Q. Now doctor I really don't know how to pronounce this, I'm told Wemacher [ph], Wemaker [ph].
A. I know the paper you referring to.
Q. Okay. I'll try and, I'm told it's Wemacher, but --
A. This is the WHO study?
Q. Yes.
A. Yes.
Q. That's -- the authors conclude in that paper, they also make a comparison, strike that. In the Wemacher paper they note this issue of confounding by depression; do you recall that?
A. I'm sure they did, yes, this is a very recent paper.
Q. All right. And in fact if we just take a quick look at it. If you go to Wemacher, Wemacher, let's take a look at page 8, the second paragraph. Actually Wemacher page 8 the bottom of the first paragraph, sorry, oh, yes, you have it. You are ahead of me.
A. I have the paper. I'm at page 8, yes. The pages aren't numbered in the binder that's --
THE COURT: So, it's up to discussion?
THE WITNESS: It's discussion section, yes.
MS. YATES: Yes, sorry.
BY MS. YATES:
Q. It says, our finding of nonspecificity by SSRI type is

compatible with a mechanism of teratogenic agent being one that is common to all SSRIs and is also compatible with confounding by depression as indication -- depression as indication or other associated factors or exposers. Did I read that correctly?

A. You read it correctly.

Q. And then they go on to actually cite if we go to the second paragraph the very three studies we just discussed; right? Jimenez-Solem, Ban, and Huybrechts?

A. Correct.

Q. And they say recent studies paragraph 2. Recent studies have suggested that the association between SSRI and CHD may be explained by confounding. Did I read that correctly?

A. That's what they wrote, yes.

Q. All right.

A. Now, of course if you continue down the paragraph they come back into this discussion about confounding by indication. If you move over in your highlighter to the start of the first paragraph on the right column, they say further investigation of the hypothesis that the causal association is with the underlying depression as necessary taking into account the specificity we find in relation to types of CHD and other CA, congenital abnormality. The evidence that maternal depression increases congenital anomaly risk is

lacking. So, that link being missing undercuts the confounding by indication argument, because you would need to have a demonstrated association that being depressed increased the risk of these specific birth defects.

Q. Okay. But you agree that the researchers should be looking at this confounding by indication, that's important, right?

A. Yes, absolutely --

Q. And in fact some of the earlier studies, you know, Petersen, Cornum, they made statements they were concerned and they addressed the issue that our results could be due to confounding; right?

A. And particularly confounding by indication, yes.

Q. Right. And then we get these later studies that say, well, let's look at that; fair?

A. That is correct. And we saw from Huybrechts when she adjusted that and 1 attempt by restricting to women with a depression diagnoses that the odds ratio did overstate when you ignored it by about 10 percent, so that's what we see. That's the best evidence we have to date in as you said the largest U.S. study about the impact of confounding by indication. Now, confounding in general can often annihilate an odds ratio can take it from 2 to .5 if you get a strong enough confounder so there's -- confounding by indication is important you ought to deal with it as best you can, but it

doesn't as yet as far as we know it doesn't have a major impact. It reduces the odds ratio down by about 9 percent and then other confounders also reduce the odds ratio down a little bit as demonstrated by Huybrechts but again, not very much. Almost statistically indistinguishable. In fact if you read my text I'll say we tend to ignore confounding adjustments that are less than 10 percent, because there's noise associated with doing that statistically, so you have to put it in context of how big is the impact of confounding by indication?

Q. So, are you saying that you can take the result from one study where you see a 10 percent reduction due to confounding and just say, oh, it's going to be 10 percent and the other studies that had other study population, other criteria, are you saying that?

A. No, not exactly. I said, I didn't put that in my report. I put in that if you wanted as a statistician, if somebody came to me now as you're sort of hinting at and said Colwin didn't adjust for confounding, well, that could make a big impact, I agree, it could, just if I knew nothing else.

So, I go to another population where they adjusted for these confounding factors if it changed by 9 percent, I would imagine since that confounding adjustment is based on the association of the confounder with the outcome so let's say smoking, it's saying how much does smoking increase the risk

of a congenital cardiac birth defect, and it also is based on the association between -- that we would assume it doesn't change that much from population to population. And we would also -- it's based on the relationship between smoking and the exposure to Zoloft for example. How much more, how -- are Zoloft exposed women more likely to be smokers or not. That could change from population.

Q. Right.

A. But the other one probably wouldn't, so a statistician knows from doing simulations and computation that we alluded to yesterday how much of an impact could you take -- get from adjusting for confounding even though in this particular population we around able to do it. It's not a definitive result.

Q. Right.

A. It's just a sense of scaling. Are we talking about an odds ratio 1.9 going to 1? All I'm saying is no. That would demonstratively be different from what the published literature shows us about the impact of adjusting for confounding by indication. And for confounding by indication as we've just said, its predicated on the idea that depressed women have an increased risk of cardiac defects which is the Wemacher paper we just read, there is no evidence of that, so then you would say, well, the little bit, it's not surprising that Huybrechts only found a little change in the odds ratio

when she adjusted for confounding by indication.
Q. I'm not going to go back to those studies. Let's switch topics. Doctor, you referenced a Pfizer internal e-mail from April, I think April 7, 2014, do you remember that?
A. I think there was an internal e-mail that came out at the time of the Frye hearing and also at some, the periodic safety update report and then subsequently some updates of that, that's my vague memory.
Q. Okay. Doctor let me focus you. I think yesterday you mentioned an e-mail from April 2014; do you remember that?
A. Well, it's fine if you want to put it up, that would be great to refresh my memory.
Q. Well, let me just see if I -- it was from Dr. Katsopolis [ph].
A. Okay.
Q. Okay. And it was part of that literature review that was ongoing.
A. Yes, that she was doing, yes.
Q. Doctor, you're not relying on those internal Pfizer documents to form the bases of your opinions; correct?
A. No. As I testified yesterday directly to Mr. Zonies I didn't actually see those documents until my report has been written.
Q. All right. And you now know that that e-mail was part

of the beginning of a review and you ultimately when you saw the final conclusion you disagreed with Pfizer's conclusion of no increased risk; right?

A. I do.

Q. Okay. And you know that that was a part of a back and forth with the FDA and reviewing the literature and it took several months to compile; correct?

A. I don't really know the internal details of how Pfizer was corresponding with the FDA about the issue.

Q. All right. Let's go to your forest plot sir, and the current one that you showed in court my guess is --

A. That's the one that was blown up today? Okay.

Q. This is --

A. Okay. So that's, that one.

Q. Blown up and I'm going to, had my team is going to watch me make a complete [indiscernible] of myself?

A. Finally a gentleman rises to his feet.

THE COURT: You can get away where saying that I can't.

THE WITNESS: I'm just the statistician.

THE COURT: Since I have two of these lovely blowups, I'm going to give one to the witness.

THE WITNESS: Thank you. Thank you very much, I really appreciate it.

THE COURT: I think that's even easier than

looking at that?

MS. YATES: I think it might be. Thank you Your Honor.

THE COURT: I will take the one that is sitting on the desk, thank you.

BY MS. YATES:

Q. All right. So, doctor, just to orient us here, we have at the top the statistically significant findings and they're in red; right?

A. Correct.

Q. Okay. And we've got Berard 2015 on there, but there's certainly some question about Dr. Berard findings; right?

A. In your mind, yes. As I pointed out at deliberate length yesterday. I see no reason at this point to put her findings on any different footing than any other, because I understand the method she used, no one else seems to, but I do.

Q. Okay. All right.

A. So, I wouldn't circle it in red and take it out. So, if you can erase that that would be helpful.

Q. My circle doesn't mean I'm taking it out?

A. Oh.

Q. I was just talking about it.

A. Okay.

Q. Berard's finding is all septal; right?

A. Correct.
Q. All septal was the result that we debated based on her abstract in 2013 using the same method has a nonstatistically significant finding and her published result using the same method according to her own documents has now a statistically significant, we debated that this morning; right doctor?
A. Yes, and that description of it is a little inaccurate, it all hinges on using the correct statistical analysis approach and you would expect the results to be different.
Q. Even using the same method twice?
A. No. If you use the same method, but in the published paper I don't compare with the abstract, because if we'd start using abstracts then the Laweek abstract has a significant odds ratio for all septals. So if you want to go to abstracts let's bring the Laweek one out, but I would prefer to stick to the published peer reviewed paper finding and their discrepancy that we debated can be explained by her explanation that's as written in the paper is this use of this required additional statistical software method.
Q. Okay. Even though she says she also used that in the abstract?
A. Well, let's going back to want abstract. So I prefer to stick to something that went through the peer review process. I change papers during the peer review process myself as reviewers point things out, so I would prefer to

stick just to the published, otherwise, I say, we bring in Laweek's abstract.

Q. And as you said, you can't verifier it, we're taking Dr. Berard's word?

A. Well, I can't --

Q. We're going by what's in the paper and Dr. Berard's word?

A. I can't actually verify any of the numbers on those, on that chart --

Q. Okay. All right.

A. -- personally.

Q. So, if we also look at your statistically significant findings seven of them are Danish studies; right? So we have Jimenez-Solem, Cornum, Petersen. Jimenez-Solem, Cornum, Jimenez-Solem, Jimenez-Solem; right?

A. These are the Danish studies; correct.

Q. All right. So, seven. Seven Danish. And let's look at all cardiac.

A. Well, do you want to point out there that there's one American, one Australian, and one Canadian.

Q. Not really. Not really.

A. Okay. Then I'm just --

Q. I'm going to Denmark right now.

A. Okay. Oh, I see, you're just focusing on the Danish studies, okay.

Q. Yes. Just --
A. Okay.
Q. Let's look at all cardiac, doctor. All cardiac is also only Denmark studies that's Cornum and Jimenez-Solem; right?
A. They're both the Danish studies, yes.
Q. Okay. And if we go to let's see, here severe CHD Wemacher.
A. That's there.
Q. Right?
A. Yes.
Q. That's the object severe CHD; right?
A. Yes.
Q. Wemacher, Epstein's anomaly; right?
A. Right. The severe CHD which is a subset of looking at very severe cardiac birth defects wasn't reported by any of the other authors though some of them talk about doing that analysis.
Q. And Wemacher actually had an all cardiac.
A. Its right there in front of you where you're pen is.
Q. Right?
A. Yes. There it is.
Q. And that was not statistically significant; right?
A. That is correct.
Q. Okay. And let's stick with our statistically significant. Colvin and we now know that was not adjusted but

that had others congenital anomalies of the heart; right?
A. Yes. And that has an odds ratio of 3.8, so that's where the discussion about the un-adjustment [ph] is important because if you think about a 10 percent change in that odds ratio that would bring it down to 2.7. It would not influence the significance nor really the impact of that study.
Q. Well, actually doctor, you said 3.8, it's 3.08?
A. Sorry, 3.08 yes.
Q. Yes. And then that leaves us with Berard that we already discussed; right?
A. Correct. Berard has a significant result for all septal.
Q. All septal. And previously where did Luick go? Luick all septal used to be in that category; right?
A. Yes. So, I moved if down because of the change that we've discussed at length of the left-hand confidence to include 1.0.
Q. And Berard on the all septal finding has replaced Luick, that's it. That's [indiscernible]?
A. I wouldn't say it's replaced it. It came in as a different paper, but Luick had to move down because of that change.
Q. On your chart?
A. On my, on this visualization, yes.
Q. Right. And I counted 59 total entries on that forest

plot, sir.
A. There are, that's the number 59 at the top.
Q. 59, right?
A. Uh-huh.
Q. And out of 59, 48 are not statistically significant?
A. That is correct. That's apparent from the colors on the visualization. Only the red ones are statistically significant at the upper right-hand corner.
Q. And you will agree sir, that most of the studies that are represented on the forest plot are repeated multiple times?
A. Well, of course, they're repeated because that particular visualization as I indicated yesterday contains not only all cardiac, but also all reported subcategories of cardiac, and so the same studies are repeated as you've pointed out.
And also it contains the overlapping studies as we discussed both yesterday and today which partially overlap with regard to the Danish that they completely overlap in regards to one of the American studies the Alwan and Rufhaus [ph] and the Swedish, the Reese Collen [ph] and Collen studies. So yes, it's just a visualization.
Q. Okay. Now doctor while you've in terms of observational studies you agree, doctor, that there are typically some limitations and caveats with respect to the

data?
A. That is correct.
Q. And you agree that it's good practice to reflect the necessary caveats when presenting the data; right?
A. Correct.
Q. You wouldn't want to overstate a case that you're making against a medicine; right?
A. No, I try to be as conservative actually.
Q. All right. And particularly when you're serving as an expert in litigation; right?
A. Actually I don't make any difference to my methodology when I'm working at Berkeley or working here.
Q. All right. But you actually have been accused of overstating the case in the medical literature about a drug in which you were testifying as a paid expert; right?
A. Are you referring to the Statin case?
Q. Yes?
A. Well, actually I haven't testified yet. I filed a report about statin, yes, but this paper was actually unrelated to the litigation work, but so they are unrelated. I did of course disclose the fact that I was working on Statin's for a separate reason when I wrote the article for the British Medical Journal.
Q. And you disclosed your competing interest, right on that paper?

A. I did.
Q. And you published an article in the British Medical Journal entitled Should People at Low Risk of Cardiovascular Disease Take a Statin; right?
A. I did with some co-authors, yes.
Q. Right. Yes, John D. Abramson is the first author?
A. Correct.
Q. And then published the paper in October 22, 2013 if you remember?
A. I don't remember the date, but it was roughly around then, yes.
Q. All right. And at that time you made the appropriate disclosure because you were an expert working with plaintiff lawyers in the statin litigation; right?
A. I had been engaged. At that point I hadn't written any reports. I now have written some reports on statins.
Q. And do you recall that about four days after your article a response was submitted to the journal raising concerns about your interpretation of the data?
A. I certainly do remember.
Q. Dr. Emmerit Decar [ph]?
A. Yes.
Q. All right. And Dr. Decar said one of the points in your article was not conclusively backed up by the details evidence and references presented; correct?

A. That's what he claimed, yes.
Q. And he said do not overstate the case against statin, sir; didn't he?
A. He may have. There were, I think several hundred comments on that paper, so I don't remember each one of them verbatim. I'm sure you've found the interesting ones.
Q. The bottom line, sir, after some back and forth and at first you disagreed that you'd overstated the case, you actually withdrew a statement from the article; correct?
A. We modified it, we corrected a statement in the article, yes. And I can certainly explain the statement if you would like, because there's been some very recent writings that will bear on that if you wish.
Q. And in your correction you stated that your article did not reflect necessary caveats and did not take sufficient account of the uncontrolled nature of the study; right?
A. Yes. That was the key issue that the reporting of certain side effects associated with all statins. I don't want to alert, upset the Pfizer Lipitor people in the room, but all statins -- the number we refer to which was from the published peer reviewed literature was a number that did not come from a controlled study and in reflection when people called us on that we thought it better to point that out as a limitation of that figure.
Q. So, you were accused of overstating the case against

statins. You corrected your paper in response?

A. We didn't correct the overstatement, the number, I think it was 19 percent of people on statins suffer from some form of myopathy, you'd have to go back to be absolutely precise, so don't quote me.

That was coming from a published paper where it said 19 per or something like that. But we didn't make it clear enough to the reader which we regretted and corrected that that was an uncontrolled study so it wasn't like a controlled clinical trial with people not on statins. So, maybe that number is too high. I do want to say and there was a big investigation of it and that correction was judged by the journal to be perfectly adequate.

The New York City Times on Sunday published the number of people on statins, I'm not claiming the New York Times is the New England Journal, but they published a figure saying that 25 percent of people on statins suffer from some form of myopathy or muscle pain.

So the issue here was bringing to the attention of the reader that that number comes from an uncontrolled study, not a controlled study. That was the paper we were referencing in the literature.

Q. Right. The statement you withdrew was about the side effects and the percentage they occurred in and it said, "The article did not reflect necessary caveats and did not take

sufficient account of the uncontrolled nature of the study."
A. Yes, I just explained that was the caveat. The number itself was not wrong. It was just that one might over-interpret that without realizing it's coming from an uncontrolled studies.
Q. Right. And in at least, certainly Dr. Decar's opinion you overstated the case against statins based on an uncontrolled study; right doctor?
A. That was his opinion, yes.
Q. Okay. Now, doctor, you are aware that there are certain medical and scientific organizations who have either put out position statements or prepared papers on Zoloft; that is right?
A. Yes, and Mr. Cheffo I think summarized them very well on his opening.
Q. Right. So, let's take a look at some of those. You know, sir, that I think you learned about it in this hearing that the FDA has just proposed some labeling; right?
A. Yes, I think Mr. Cheffo put that statement up on the screen on his opening.
Q. Right. And the FDA relies on multiple, or refer to multiple studies; right?
A. Well, if we could put the statement up, I think it might be helpful to see what explicitly they said.
Q. Sure. Let's do that?

A. I think Mr. Cheffo put it up, so you should have it right at hand.

Q. Let's go to FDA proposed label, tab 235, Roger, please. And we're at page 11 to 12. And to be fair --

THE COURT: Is this in a binder.

MS. YATES: It might be, Your Honor. If it not I can use the [indiscernible]. Let's do the [indiscernible].

MR. ZONIES: Your Honor, I'm going to object to this line of questioning because it has nothing to do with methodologies presumably we're going to see some conclusions reached by these organizations and it has nothing to do with Dr. Jewell's methodology, it's about conclusions. Unless we're going to go into the methodologies of each of these and compare those to Dr. Jewell's since I doubt we are and I hope we're not.

And then secondly, this correspondence with the FDA, we've requested from Pfizer the correspondence with the FDA that led up to this proposed label, because IT may be just Pfizer's proposal to the FDA and we don't know and if it's -- and we don't have that correspondence yet. Pfizer hasn't provided that to us. And so --

THE COURT: All right. And I know this isn't part of the report.

MR. ZONIES: And it's not part of the report.

THE COURT: Ms. Yates would you respond police

to why you are pursuing this course of questions.

MS. YATES: Yes. Dr. Jewell disagrees with these organizations and our point is you can't follow a reliable methodology and reach a different conclusion, because everybody else is on the same page. So, I can do this very quickly, Your Honor.

THE COURT: The methodologies you are referring to that apparently he doesn't agree to how do we know that he doesn't agree to them?

MS. YATES: Well, I think the point is the [indiscernible] versus Merrell Dow Pharmaceuticals case, Your Honor. When I scientist claims to rely on a method practiced by most scientists yet presents conclusions that are shared by no other scientist, the District Court should be wary that the method has not been faithfully applied.

So, while I -- all of these organizations looked at the literature; right? I can't be more detailed in terms of what they did, but several of them and I know Dr. Jewell has criticisms of their methodologies, but their reached certain conclusions based on those methodologies. Dr. Jewell disagrees with them. And it is this very case that says, I reviewed the literature, I rely on the literature, I conclude X. You can't all going down the same road if everybody else is on a different page.

THE COURT: But everybody else being on a

different path is a conclusion. How do I apply that to his methodology?

MS. YATES: Because you can't get to Dr. Jewell's conclusion if you have a reliable methodology.

THE COURT: And how are you going to present that other than presenting these other scientists?

MS. YATES: I'm going to present these other scientists' conclusions and argue it, Your Honor.

THE COURT: Mr. Zonies, you want respond? You're still on your feet.

MR. ZONIES: Yes, that's the issue, Your Honor. If Pfizer would like to bring the AHA in here and allow me to cross-examine them on their methodology so we can understand them and then compare their methods to Dr. Jewell's methods I'm not averse to that, but this is essentially trying to use a proxy out of court expert organization whom as we've showed in opening, whom first of all Dr. Jewell does not rely upon, because it's just a conclusion, the oldest conclusions a single piece of paper, one page and based on two studies or four studies. So, absent my being able to cross-examine them on their methods and show how we believe them to be, but it's speculation on our part, we believe them to be terrible methods, it's really not relevant here.

That case is talking about the underlying studies and making an examination of the studies and the

methodologies. It's not talking about whether or not the AHA in a one-page paper or the Otis in a one-page paper reach a different conclusion. We'll stipulate they reach a different conclusion. There's no need to go through a whole process of it, because that's all that's going to be shown is their --

THE COURT: All right. Just let me clarify, because that makes sense to me. Let me clarify. Are each of these proffered studies and organizations that reached different conclusions based on different methodologies than Dr. Jewell, did each of them comment or critique Dr. Jewell's methodology and his report? In any of them?

MS. YATES: I doubt that -- not specifically, no, Your Honor, I doubt they've heard of Dr. Jewell unless they've read his EEG paper.

THE COURT: All right. So this is really the classic issue. The battle of experts who are not here and haven't submitted their work to be reviewed as Dr. Jewell's have.

MS. YATES: Well, let me clarify one thing, the FDA current thinking on our label is not peer reviewed all of the others are peer reviewed and statements out there in the medical and scientific community for doctors and practitioners and ladies deciding whether to take this medicine during pregnancy review and rely on. So they followed a methodology that's Otis, Your Honor, it gives advice to patients. Their

methodologies have pursed peer review with the advice and statements they are giving. That's in contrast to a statistician who is in a courtroom and I think there's courtroom versus peer review real world. And that the Court should be aware of that.

THE COURT: But that's more argument than anything else. It's not the evidence that counters the statistician who's here before him. It's like putting up an epidemiologist against a statistician. One have a better conclusion than the other, but it's really about his area of expertise if he is doing it in a reasonably applied way.

And the FDA labeling is a whole other part of the case that we've never gotten into in discovery or anything else. Labeling changes have a hierarchy and I went through this in Avandia and a process that is foreign to most people and it would be totally unfair to say FDA's going to do this or has done this is. That's not what he wrote on.

MR. Cheffo: Your Honor, if I could just address just a few quick things, because I think we may have gotten -- because I think there are a few different issues here. The first is everyone, the whole point of what Dr. Jewell has told us; right, is that he wishes he had a team. When he works in the real world he has team. His team is study authors; right?

We don't have any of those people here; right? So the nature of kind of what we're all doing here is we have

to rely --

THE COURT: Not to interrupt you Mr. Cheffo --

MR. CHEFFO: Sure.

THE COURT: All these studied authors are in the record in terms of their materials, their studies and he's explaining repeatedly so how he's utilized them or ignored them.

MR. CHEFFO: And we -- and you're absolutely right and the point I guess he is that he has taken what other people's work is outside the courtroom where none of us can take their depositions they're not here and the point is what we're examining I believe and asking Your Honor to examine is whether his methodology in reviews and analyzing that independent peer review data meets the Daubert standards; right?

So, what we're doing is looking at that and we're looking at other organizations who are learned, who are reliable, who've looked at that sim information and applied the same methodology or a methodology and determined if it's appropriate. So, where I think it's fair and this is exactly I think what Your Honor did with respect to Dr. Berard too, and I guess there's two other quick things.

THE COURT: But --

MR. CHEFFO: First is the --

THE COURT: I have not pass judgment as to the

standard of Daubert on any of the studies that have been relied on in here, nor could I.

MR. CHEFFO: Agreed.

THE COURT: And how can I do the same with your organizations, however great a reputation they may have.

MR. CHEFFO: Well, I think the issue is this is, Your Honor, Daubert, one of the factors I'm going to show this I think in one of the first slides; right? General acceptance is not something that is required like it may be under [indiscernible] Frye or [indiscernible] but it's certainly a factor; right?

So, it's perfectly appropriate for Your Honor to consider both from the Lusk [ph] decision and from Daubert and it's progeny whether in fact these kinds of analysis, this methodology is generally accepted. It's, again, it's not the end all and be all, but it is certainly a relevant factor and I would say the one thing about the FDA, the plaintiff's started this story in a number of way, right? They put in and they wanted to have and they've done this and in certain hearings and at trial and in Dr. Jewell's report they took two lines from or two entries from Dr. Katsopolis and then they also took the PSURs. That was part of a story; right? Essentially you remember from the opening, Your Honor, the FDA asked for some information there was an initial review. There was a subsequent amount of work for five or six months,

plaintiffs have got all this information. They've given all of that information. Then ultimately Pfizer in response to the FDA which was the beginning story was the documents that they've relied on, Pfizer then submitted information in January of 2015, all of that information has been given to counsel, in fact we've told them that we've done searches for any information between January and August.

Now, it's just I think by fortuity that the hearing got moved to our knowledge and we're confirming this with counsel and have told them this. There's been no other back and back and forth that was the first information. We got the information and within a very timely basis it was a proposed labeling which you saw earlier that was given to plaintiffs.

So this idea that they don't have the information is not really accurate, but it's all again to the point here, Your Honor, is that the story about whether you can look at one little piece of the puzzle, the FDA has now looked all the information. They have the same information that Dr. Jewell does that everybody else does and they've basically come back and said looking at that, here's what we think the appropriate labeling is. So, I think it's absolutely appropriate for Your Honor to consider it as part of your Daubert analysis.

THE COURT: Let me hear from you Mr. Zonies on

the FDA.

MR. ZONIES: Yes, I mean, I'll read the e-mail from Mr. Cheffo's colleague sent to me on the 27th. To follow up on this, we have requested all correspondence back and forth between the FDA and Pfizer that led up to this proposed label, because we don't know whose proposal it is or what the back and forth was and Mr. Lafadda [ph] sent me an e-mail on the 27th saying to follow up on this. I estimate the production from this file would go out late next week which is after today so there appear to be documents according to Mr. Lafadda, it's the first I've heard that there aren't and that we're supposed to get those documents after the hearing today, because we didn't think that necessarily because we believe that this was not at all particularly relevant to Dr. Jewell's methodology we didn't come to the Court and say, oh, we should postpone, because this is what the FDA does or doesn't do frankly in the context of a Daubert hearing about his methods means very little in --

THE COURT: And to propose to question him on the as yet proposed, but probably some change in a label approved by the FDA or not seems to me to be throwing hypotheticals out.

Now there's a certain amount of that you can do in a Daubert hearing. But is this fair? And is it relevant to my Daubert analysis if the FDA is changing the label now?

That nobody else on the plaintiff's team has dealt with yet.

MR. CHEFFO: Just to be clear on this, the FDA is not -- that's the point the FDA is not changing the label. The FDA is saying hey, we've looked at this it's a category C, should there be something about the -- the plaintiff's whole position has been, hey, Zoloft's a teratogen, you should warn that it causes birth defects.

The FDA's now looked at all of this information and they've basically come and we can put those back up, I know Your Honor probably saw those quickly, they're saying we don't think there is a labeling change required. In fact, we've looked at all the literature and there's no teratogen so for the Court to basically not account for the fact that that what Dr. Jewell is saying is against the entire of the world and now the FDA is saying it seems to be absolutely relevant for a Daubert analysis, because nobody is saying and it's not unfair because they've -- we've got it the same time that they've gotten it.

THE COURT: It's how you're doing this Mr. Cheffo. It's the middle of the Daubert hearing, it's towards the end of the Daubert hearing. And all of a sudden this hasn't been briefed, this hasn't been really noticed in time. We only extended the time here because of the Luick changes and I'm really concerned about some kind of fairness. I want all of the information out. This isn't accounted for in his

report from what I know.

So, the question is can you ask him in a Daubert hearing about an FDA label change or refusal to change when his findings don't happen to agree with Pfizer's?

MR. CHEFFO: I would just say this, Your Honor, just in terms, because I hear you and I understand --

THE COURT: It's a hypothetical, really.

MR. CHEFFO: Well, I don't know that it's a hypothetical to address the fairness point and again, I'm not faulting counsel for this we specifically said, because this was, you saw April 12th I think is the date of this we gave it to counsel right after and we, or I'm sorry, August, thank you. And we specifically -- the 14th, it could be. I have my -- Verizon network is keeping me honest here.

And basically we said to the -- we gave it to the PSE and we said hey, tell us now a week ago. Tell us now if you want to go and tell Judge Rufe that you need more time for this and if so we will do that. And I don't think there's any dispute about that. And PSE said, no, we don't want more time. So, they frankly have what we have. I did tell and Paul Lafadda is looking if there is any additional information, I've told them also, I'm not aware of it, it's not like we have anymore. If we find it in files we will produce it. And again if they want to supplement, if there's something that they want to do that's fair. We're not trying

to basically pull a gotcha, but remember this is a process, the FDA started, they asked March of 2014 then in September and October there was a submission then in January. It's the FDA that basically just on August 14th said we've look at the information, we don't think that there should be any change. And I think again for the purposes of evaluating whether it's generally accepted -- is a methodology that finds that Zoloft causes all birth defects consistent when the FDA says, hey, don't change your label, that's something that we think that Your Honor can and should evaluate as part of its decision.

THE COURT: There is much litigation about FDA label, its adequacy and correctness and right now you're going to try to ask an expert who has been called by an opposing party to start testifies outside his report which would not be allowed if Mr. Zonies tried to ask that question.

And that's a big problem to me. Where are you going with this with all of the other as yet unnamed but some of them have been named so-called authorities that allegedly agree with the FDA, it's too much, it's too attenuated. FDA may not be attenuated because that has been in the works, but their conclusion hasn't been and I want to be fair here and only elicit evidence that should be admissible.

Now, I think it's perfectly reasonable to say here's the label it's not what your conclusion is can you please explain the difference and how do you explain that

other people don't agree with you? I think that's okay. But where I think Ms. Yates was lining things up was a whole list of different methodologies that are going to be outside the evidence in this case.

MS. YATES: I have a feeling Ms. Yates has a few new questions to ask based on Your Honor's --

THE COURT: Well, you can summarize on what the FDA is doing or not doing. If there's no agreement as to that the premise of the question is going to elicit information I can't use, testimony that I won't be able to use, but I don't want to do this again.

So, can we come up with some context here that says and I don't want to defer this. I don't think there should be a deferral of my rulings or this particular issue on the FDA. We better start getting all the evidence on the record to get some conclusions drawn here, so we can move forward whatever way that is.

Mr. Zonies, would your position change if the questions posed were confined in any way to what the FDA is currently doing?

MR. ZONIES: Well, again, Your Honor, that's the foundational issue is in part. Our concern is this -- we don't believe this was written by the FDA, we don't know if it was. Is this Pfizer's proposal to the FDA that the FDA is hasn't -- so, in your own words when Ms. Yates stands up and

says here's what the FDA's okay with, we don't know that; right? Because it's not final so, if the question is about that document, hey, this document says by the way that there are some studies that show risk do you disagree with the records in that document, I suppose that's fine, it's about conclusions, but Dr. Jewell nor opposing counsel knows anything about the methods used to reach that, so to the extent that it's a -- it's some sort of affirmation that the methods used in these various documents we're about to see are the correct methods, it's impossible for Dr. Jewell to comment on that.

THE COURT: Yes, I don't think there's a case that's ever said that, because the FDA has said so that it's correct. And I'm not criticizing the agency, we depend on them every minute of every day in many facets of our daily lives. But there is supposed to be a process here. I would need to hear, you may need to do this overnight counsel and I would need to know what precisely are the questions that are going to be posed and where are the parameters of this line of questions and I'd that postponed until tomorrow morning. Right now I'd like you to move onto something else.

MS. YATES: Okay. Your Honor then we -- this may be my last section, so if we could just take a brief recess so that I can figure out if there's more for me to cover today.

THE COURT: All right.
MS. YATES: That would be perfect.
THE COURT: That would be fine.
MS. YATES: Thank you, Your Honor.
THE COURT: We're in brief recess.
(Whereupon there was a recess in the proceeding from 3:27 p.m. to 4:20 p.m.)
DEPUTY CLERK: All rise. Court is now in session had Honorable Cynthia Rufe now presiding.
THE COURT: Good afternoon.
MULTIPLE SPEAKERS: Good afternoon, Your Honor.
THE COURT: Please be seated. Where are we counsel? Does these courtroom feel like an obstacle course?
THE WITNESS: It does a little, yes.
THE COURT: Yes, in more ways than one.
THE WITNESS: I've noticed. I'm glad I'm a statistician.
BY MS. YATES:
Q. I may have actually tripped over there or dropped something, but anyway. Doctor we're almost done?
A. Okay.
Q. Okay? Where went to your -- do you recall doctor that with your expert report you had a reliance list attached to it?
A. Yes.

Q. Is that correct? And that should be in, I think tab 1 of the binder Mr. Zonies gave?
A. Yes.
Q. And if you go all the way to the back unfortunately, it's in, I think alphabetical order. It says Zoloft label and then you've Pfizer's website.
A. Yes.
Q. So that's -- it's correct to state sir, that you have the Zoloft label on your reliance materials; correct?
A. Yes, I read the label at some point and I think I was asked about at deposition and said no I had no expertise on labeling or with the FDA.
Q. Right. You're not a regulatory expert; right doctor?
A. No.
Q. And we heard earlier today that in the hearing that in fact you had asked the lawyers to submit your expert record to the FDA; right?
A. Yes, that was a question at trial that I hadn't done that and if I felt important enough about it I should and so I asked them to do so. I was happy to be released to anyone, actually.
Q. And we just found out that the lawyers have in fact submitted your report to the FDA sometime back in June; do you know that?
A. As I indicated I asked them verbally and they said they

had done it, but I didn't have anything in writing which is what you asked me.

Q. Right. So with the label on your reliance list and your report having been submitted I assume that you have some interest in the current position or the current thinking of the FDA and the language in the label?

A. I have interest in everyone's opinion on the issue.

Q. Okay. Well, let's look at the FDA's weren't proposed language in the label; okay doctor and -- Your Honor I don't believe that this was previous marked even though there were a lot of submissions?

THE COURT: I don't think I've seen it.

MS. YATES: I'm going to mark it as Exhibit A. Defense Exhibit A to the Daubert hearing if that's okay.

THE COURT: Yes.

MS. YATES: And we will get you copies or we have copies and we will get you copies. Oh, there we go.

BY MS. YATES:

Q. So, doctor, just quickly, I just want to know when I show you certain statements made by the FDA the current proposed label whether you agree with them; okay?

Let's go to pregnancy risk summary. Doctor, overall --

A. Could you tell me the page number again?

Q. I'm so sorry.

A. That's okay.

Q. So, that's a very good question, so it's actually a bates stamped page?
A. I can manage that.
Q. Can you do that, so 3744.
A. Okay. Now I'm there, thank you.
Q. Right at the bottom, doctor.
A. Yes.
Q. Pregnancy risk summary.
A. Yes.
Q. Last word on the page, overall. Okay? Overall available published epidemiologic studies of pregnant women exposed to Sertraline in the first trimester suggests no difference in major birth defect risk compared to the background rate for major birth defects in comparative populations. I take it you disagree with that.
A. I -- no. I don't have an opinion about major birth defects.
Q. Okay. Then we read on, some studies have reported increase for specific major birth defects, however, these studies are inconclusive, (see data). Do you have an agreement or disagreement on that statement?
A. Well, it doesn't specifically mention that cardiac birth defects are one of the specific ones there related to, of course I would agree that some studies have reported increases for cardiac birth defects, but they don't state that

explicitly so I can't really comment.
Q. All right. Let's move to page 3745; right? At the bottom of the page, first trimester exposure.
A. Third -- first.
Q. First trimester exposure.
A. Oh, it starts and then it moves onto the next page.
Q. Yes.
A. Yes.
Q. Okay. Are you with me?
A. Yes.
Q. Starting with the second sentence, "A meta-analysis of studies suggests no increase in the risk of total malformations summary odds ratio 1.01, 95 percent confidence interval .88 to 1.17 or cardiac malformations (summary odds ratio .93, 95 percent confidence intervals .70 to 1.23 among offspring of women with first trimester exposure to Sertraline.) Do you agree or disagree with that statement?
A. Well, that is actually just a descriptive sentence about a meta-analysis. It's parent from Mr. Cheffo's slide and from the numbers that is in fact referring to the Miles meta-analysis as I've now testified at length, I do not believe that the Miles meta-analysis gives an appropriate summary of the available data on Zoloft and cardiac birth defects and in specifically it reflects that the FDA in that sentence has not reviewed all of the studies on Zoloft and

cardiac defects that I have reviewed so I would state it twice in the arguments about this language that the FDA has reviewed all of the studies.

The Miles meta-analysis you will recall only contained five of the old studies on Zoloft and cardiac birth defects so I don't disagree with the sentence that's what Miles says, but as I've said many times now that is inconclusive or inappropriate summary of the evidence for the reasons that it's got a lot of heterogeneity masked by the averaging and it's only covers five studies.

Q. Well, so just because the FDA references Miles for that point doesn't mean that they haven't reviewed the other studies.

MR. ZONIES: Your Honor, I just want to clarify the record and this was one of my concerns that as the law provides and as we all know the FDA, this is not the FDA's label, this is Pfizer's label and so we keep and since Dr. Jewell's not an expert in this, he may not know that this is actually Pfizer's language and not the FDA's, so I just want to be clear on that.

MS. YATES: No, I need to be very clear, Your Honor. This is what came to Pfizer from the FDA. This is the FDA's proposed language.

MR. ZONIES: This was my concern about not having a foundational required -- if we could just say this

language in this proposed label and not attribute it to being the FDA saying it I'm fine with that, because this is not the FDA's language. The law makes it clear that the label is Pfizer's label and they're responsible for it. That was my only concern.

THE COURT: And will you accept that premise?

MS. YATES: I will.

THE COURT: Because I think it permits you to continue this line of questions without the underlying conclusion that the FDA has written this.

MS. YATES: Fair enough, Your Honor.

THE COURT: Thank you.

BY MS. YATES:

Q. Dr. Jewell just one more section of the label and then it again deals with cardiac. Let's go to the next tab, please, same page, doctor, right after where we were.

A. Yes, I'm with you.

Q. Okay. And increased risk of congenital cardiac defects specifically septal defects the most common type of congenital heart defect was observed in some published epidemiological studies where first trimester Sertraline exposure, however these studies were limited by the use of comparison populations that did not allow for the control of confounders such as the underlying depression which may be independently associated with these malformations. I take it that you

disagree with that statement as well.
A. Well, I don't disagree that an increased risk has been found in some published studies. I do agree that some studies were limited by the inability to adjust for confounding my indication, but some others were not and I do not believe it's a fair summary of the entire data to say that the observed increases in risk that are in all of the studies are washed away by dealing with confounding by indication as I've previously testify.
Q. Fair enough. Doctor, also on your reliance list is the scientific statement by Denofrio et al.
A. Yes, I see that.
Q. And that's the scientific statement -- well let me just give a little bit more detail it's from the American Heart Association. Adults With Congenital Heart Disease Joint Committee of the Council on Cardiovascular in the Young and Council on Clinical Cardiology. Council on Cardiovascular Surgery and Anesthesia and Council on Cardiovascular and Stroke Nursing, the title is Diagnosis and Treatment of Fetal Cardiac Disease: A Scientific Statement from the American Heart Association, did I read that correctly?
A. You did.
Q. So, that scientific statement is on your reliance list and you've been asked questions about that statement; right?
A. Yes, the Pfizer lawyers have ask me about that a couple

times.
Q. And you're critical of the fact that they only site to two Zoloft related studies in that scientific statement; correct?
A. That I can't recall I'd have to go back and look at the statement to refresh my memory.
Q. Okay. Were you listening to Mr. Zonies, because I think that's what he said?
A. I actually, my opinion doesn't, I don't listen to Mr. Zonies for my opinions. I've tuned them out.
MR. ZONIES: Objection, Your Honor.
THE COURT: Overruled.
MS. YATES: I'm sorry, I think I have to end on that, but I do have a couple more questions.
THE WITNESS: Okay.
MS. YATES: I timed that wrong.
BY MS. YATES:
Q. Doctor, you will agree that that statement, their conclusion, you disagree with their conclusion?
A. I don't remember the conclusion. That was a -- what my memory tells me was that was a statement about the treatment of fetal cardiac disease and was dealing with the issue of whether infants whose mothers were exposed to Zoloft should be screened more heavily because of the concerns about the potential risk of Zoloft increases certain kinds of birth

defects. That was my memory, but to say it, to be fair to it if you really want to ask me questions we should look at it in detail.

Q. Yes, I apologize, I was trying to short circuit. Let's go to the AAHA page 8, please and just take a quick look at the results.

A. When is that?

Q. That is a very good question. That is, I don't know if it's in your binder.

THE COURT: It's in your binder.

MS. YATES: It should be. [Indiscernible].

THE COURT: Number one. That is in Pfizer's binder.

MS. YATES: First tab, I believe.

THE COURT: Yes.

THE WITNESS: This is the Denofrio.

MS. YATES: Yes.

THE WITNESS: Yes, okay. I have it.

BY MS. YATES:

Q. The scientific statement. Doctor, the results -- so selective serotonin reuptake inhibitors, the use of SSRIs in pregnancy has been investigated, I assume you agree with that?

A. Page number, please.

Q. I'm sorry.

A. That's okay. I just don't know where you are.

Q. Page 8.
A. Eight, thank you. Yes, okay.
Q. All right.
A. Now, I'm with you.
Q. SSRIs, the use of SSRIs in pregnancy has been investigated. I assume you agree with that?
A. It has been investigated, yes.
Q. Okay. Results indicate that there is no increased risk of CHD associated with the use of most SSRIs although Paroxetine may be an exception, did I read that correctly?
A. You did.
Q. And I take it you disagree with that?
A. Well, it's not specific about Zoloft, I mean my opinion is absolutely clear about Zoloft, they don't mention it and I assume that you would put that in the category of the new increased risk and then I would disagree with it.
Q. Okay. Right. And so most --
A. But not the Paxil.
Q. Right. They say no increased risk. Most SSRIs and then they actually separate out Paxil may be an exception; right?
A. Well, I don't know if they think of any others as being an exception, I don't know.
Q. They certainly don't state it; right?
A. No. They don't say all but one, they just say most.

Q. And then the only one they site to is Paroxetine which is Paxil?
A. That is correct.
Q. Okay. Doctor, another article on your reliance list is by Dr. Refuse et al.
A. Could you say that name again?
Q. I'm saying it the way I said it, but I've heard her say it and it's nothing like this, but it's Refuse?
A. Refuse, yes.
Q. Refuse. Good.
A. And that's in your binder too, right.
THE COURT: Same book.
BY MS. YATES:
Q. Yes. Thank you.
A. Okay. Yes, I have it, I see it at least.
Q. And this is -- let me know when you get there.
A. Yes, I have the paper open and now in front of me.
Q. Perfect, and it's specific SSRIs and birth defects: Basion Analysis to Interpret New Data in the Context of Previous Reports. That's a title; right?
A. Correct.
Q. And it was published very recently accepted for publication May 29, 2015?
A. Yes.
Q. And if we turn to page 2015, I'm sorry, page 4.

Doctor, it shows that Zoloft was the most commonly SSRI when the study was done; is that right?

A. In this population, that is correct. This is a U.S. population.

Q. In fact, the study was funded by the Centers For Disease Control and Prevention; right, the CDC?

A. I'm not familiar with the funders of the study it probably says somewhere, but --

Q. Right. Let's go to page 8.

A. Oh, there we go.

Q. Okay.

A. The data collection was funded, yes.

Q. Right.

A. I don't know if that refers to just the MBDPS whether that's funded by the CDC or whether they funded the study. It actually looks like it's just the data itself.

Q. The data collection?

A. Yes.

Q. All right. Are you aware, sir, and you've reviewed the study it's on your reliance list?

A. Is it on my reliance list?

Q. You did a supplemental reliance list dated August 13, 2015.

A. Okay. Well then it's, I know it's very recent that I've seen it, so I was confused because you were referring me

back to the reliance list for my report and it couldn't -- I didn't think it could be possibly be in there.

Q. Right. So this is a supplemental list, I'm sorry.

A. Okay. All right. So a different document. Okay. That's fine.

Q. Okay.

A. I've certainly seen it, so --

Q. All right. And you are aware, sir, that in fact the CDC has posted the key findings from this study on their website; right?

A. No. I haven't actually looked at the CDC website in the last week since I've seen this paper.

Q. All right. Well, let's see if you agree with some of the postings on the CDC website based on the study that you've reviewed; okay?

A. Sure.

Q. All right. Let's go to tab 232.

A. I can't read it.

Q. Wait a minute, we're getting there doctor, I'm sorry?

A. Okay. I can't even try on that one.

Q. No. I give up too as well, doctor, I apologize and I need a page number, page two.

A. Is it in the binder?

Q. Well, that's a good point?

THE COURT: No.

BY MS. YATES:
Q. No. Sorry, can we struggle along and -- we've got it. I'm sorry.
A. Yes, thank you.
Q. So, doctor, if you go to page 2 and it says, now I've lost it. So the -- actually it's the bolded paragraph, New CDC Study Findings.
A. I'm with -- oh, you've just changed it, but, oh, okay. Yes, I see that paragraph.
Q. All right. And then let's pull out. Researchers found -- what you have [indiscernible] there we go, thank you. Researchers found that some birth defects occur about two or three times more frequently among babies born to women who took certain types of SSRI medications early in pregnancy.
This analysis -- wait a minute, I'm reading from somewhere else.
A. No, you're reading what I'm reading.
Q. Am I right?
THE COURT: You're at the bottom of the page is where the pullout is from, yes.
MS. YATES: I'm sorry, I'm saying what does this study add?
THE COURT: What does this study add?
THE WITNESS: Okay. I can read that too.
BY MS. YATES:

Q. Right. Okay. What does this study add? Researchers found some birth defects occur about two or three times more frequently among babies born to women who took certain SSRI medications like Fluoxetine and Paroxetine early in pregnancy.

However, links between birth defects and other SSIs like Sertraline were not observed in the CDC study. Did I read that correctly?

A. You read it correctly.

Q. And that study is the Refuse study that we just talked about that's on your reliance list?

A. Yes. There's -- I looked -- this looks like an online press release from CDC specifically about the Refuse study.

Q. Right. It's their website; right?

A. As I said an online press release, yes.

Q. Okay. And let's go to the next page if we can where it says reassuringly. What page is it?

MR. CHEFFO: Three.

MS. YATES: Page 3, next page. Page three.

BY MS. YATES:

Q. Reassuringly, doctor are you with me?

A. Yes.

Q. What were the studies main findings as the heading, right doctor? And then the -- fourth bullet, third bullet, sorry. Reassuringly, researchers did not confirm links between Sertraline, the SSRI used most often and any of the

birth defects observed in previous studies. Did I read that correctly?

A. You did.

Q. And in fact Dr. Refuse reports the same thing in their study if we turn to page 7 of her study.

A. I'm there.

Q. Okay. Tab 230, okay. Doctor, if we go to page 7 the CDC website is actually referring to this language. It is reassuring that none of the five previously reported associations between Sertraline and birth defects were confirmed in this analysis particularly since about 40 percent of women reporting use of an SSRI in early pregnancy used Sertraline. Did I read that correctly?

A. You did.

Q. And I take it that you disagree when the conclusions of Dr. Refuse and the postings on the CDC website?

A. Well, she took this study in complete isolation and ignored almost more than 90 percent of the rest of the evidence we've been talking about, that's what this study says. This is the one study on the National Birth Defects Prevention Study where they collect the data like this. This is an update as we discussed earlier of the Alwan study. The Alwan study reported a lower association here and this study actually increased it substantially because the new data contradicted the Alwan study so I can't possibly -- knowing

that detailed analysis I can't possibly agree with this sweeping generalization in the statement, it's not based on the methodology I used which was to look at all the evidence.

Q. Okay. Thank you doctor.

MS. YATES: Thank you, Your Honor.

THE COURT: Thank you. Redirect?

MR. ZONIES: Thank you, Your Honor.

BY MR. ZONIES:

Q. Dr. Jewell, in the National Birth Defects Prevention Study do you -- that's a study -- how did they determine exposure in that study? Do you know?

A. I do in the sense that I've read it, this one relatively recently as was just discussed. They did this, if my memory is and we could look at the paper, we just had it opened, it's based on interviews with the mother at 11, you know, on an average about 11 months post-delivery, so about an average of a year and a half post the exposure period by interview and it was a very, very simplistic question. The question I think is actually in the paper if you're interested in it.

Q. So, just to be clear then the two eleven months plus nine months, 20 months?

A. A year and a half, I said to be conservative.

Q. Thank you. A year and a half after the question, the exposure, the questions asking about, so a year and a half

later they interviewed a mother and said, hey, what drugs were you taking a year and a half ago? Is that one of the -- is that how this study gathered the evidence of use?

A. Yes. They didn't have the word "hey" in there, but they said, to be specific on page 2, "Between three months before conception and the babies' date of birth and putting in the name of the baby, did you take any of the following medications"?

Q. Okay.

A. Prozac, Paxil, Zoloft, Celexa that was the entire question.

Q. And in your in depth analysis does that give you -- that you've expressed in your report, did that give you some concern about the accurate capture of exposure in this study?

A. Yes. In a lot of work done on trying to measure exposure in the accuracy of the classification of exposure using various methods, maternal interviews probably the worst of all for reasons that we could go into at length. Retrospective maternal interview, so interviewing no prospectively, that's bad enough, but retrospective maternal interview is known to be extremely inaccurate, I mean, very high rated of inaccuracies.

So most statisticians when they see that level of inaccuracy know that the impact of that on the results is it will wash out or dilute any potential association and that's

why we've moved to more accurate measures of exposure.
Q. And despite your concerns about that, you actually expressly discussed those concerns in great detail in your report.
A. I do and there are other studies that use maternal interviews and that's why yesterday when I said not all of these studies that were used in the meta-analysis or in my visualization stand with equal footing, because they measure exposure differently and that makes a big difference.
Q. And despite those concerns you didn't hide from those studies, those results are all in here; correct?
A. Yes. I believe Refuse should have been added to this somewhere. Yes, it's there.
Q. Yes.
A. So, it's there.
Q. Okay. And you take that into your analysis as you said of the whole data and that's part of what you --
A. That's part of the methodology, but you have to look at the issue of bias and how exposure is measured. We haven't talked about it a great deal, but it's a very important part of the puzzle.
Q. Now, Dr. Jewell on your cross-examination you were asked about the conclusions of some of the study authors; do you recall that?
A. I do.

Q. And one of them was the Bond Study in 2014?
A. Yes, in the U.K.
Q. And that was a depression restricted analysis, in other words it had women who were depressed on both sides of the equation?
A. Correct.
Q. And you were showing this quote from the abstract at the beginning of the paper; right?
A. Yes.
Q. And it says overall MCA risk and I think you pointed out what does MCA mean?
A. Major congenital abnormality.
Q. So, MCA risk did not increase with maternal depression or with antidepressant prescriptions and I think you also discussed that that's talking about the all SSRIs; right?
A. Correct.
Q. Is that relevant to your analysis, MCA risk with all SSRIs?
A. No, because I want to be very specific about Zoloft and not assume that there's a common effect for all of them. It's relevant to the extent that the antidepressants that are lumped together show no increase because for there to be no confounding by indication they should be at increased risk, because they're suffering from depression, but as I state in my report many studies don't find that and we've talked a

little bit about that, the absence of that evidence.
Q. And then, Dr. Jewell you actually discussed this study in great detail in your report; correct?
A. In some detail, yes.
Q. In some detail. And, but you actually -- next slide, please -- discussed the actually -- not these results which were just shown to you, you discussed these results that are about Zoloft and about cardiac birth defects; right?
A. I did, yes.
Q. This wasn't shown to you during cross-examination was it?
A. It was not. No.
Q. And you actually agree with these conclusions in Bond; right?
A. I do.
Q. And Bond seems to agree with you.
A. Well, we'd have to ask Bond but that's -- I don't disagree with this statement.
Q. And importantly, in Bond the result that they're talking about here is a 1.39 or essentially a 40 percent increase in risk that was nonsignificant in Bond; right?
A. That's correct. And I did bring that up to the opposing counsel.
Q. And yet that's the result, nonsignificant that they're saying is consistent with other results?

A. That is correct.
Q. Even though it's nonsignificant?
A. Correct.
Q. So, to test consistency here Bond certainly like you does not have a concern with methodologically looking at nonsignificant results when you're looking at all of the data; correct?
A. No, because if they had found an odds ratio of .79 they might well have written the sentence saying even though that wasn't statistically significant that contradicted earlier studies. That would've been a different conclusion, hypothetical, because that's not what happened, but I think you should look at nonsignificant results and see how they compare with what we already know in the literature.
Q. And what you just described is actually what Refuse did; right? Which was a nonsignificant finding in Refuse and they said this contradicts other significant findings?
A. Yes. They did, yes.
Q. Yes, okay. And to be clear methodologically everyone seems to think it's appropriate to look at nonsignificant results when assessing consistency, it's happening in the very papers you've reviewed.
A. It's certainly part of the evidence; correct.
Q. And with regard to overlap, do you recall some questions about overlap in a dangerous population?

A. I do.
Q. The next slide, please. You mentioned that you find there was some independent scientific data and evidence even in the -- even when populations overlap somewhat that informed your opinion; is that right?
A. Yes. I spent some time on this yesterday that particularly with the Jimenez-Solem I there's the least overlap, it's the biggest difference from Petersen and Cornum that the new data that's provided by Jimenez-Solem provides new information beyond what was in either Petersen or Cornum if to the extent that it's different that would of course contradict or not confirm to the extent it's the same it is a measure of independent replication that's most, I think relevant in comparing Jimenez-Solem's result and I talked about this yesterday so I don't know for the sake of time I don't want to repeat it, but had the odds ratios been dramatically lower in Jimenez-Solem for the new women, their overall result would've been substantially lower than what Petersen or Cornum reported. So that does provide some form of replication.
Q. And I think we looked at yesterday with Refuse and Alwan in that situation, not only you looked at the fact that Refuse must have necessarily had a 20 to 30 percent increased risk in the new women in that population but Professor Bracken another epidemiologist supported that methodology for looking

for replication?
A. Exactly, yes.
Q. And Dr. Jewell, it wasn't just Professor Bracken who's done that and you, in Cornum itself this is done.
A. Yes, Cornum itself made that point and he of course knew about Petersen, they were probably -- knew each other personally, I would imagine, both from Denmark looking -- interested in the same issues and they knew about the Petersen paper which came first as we discussed this morning and they point out that they were willing to compare the results that they got with Petersen knowing that there was some overlap, but not entire overlap because they realized they would've the potential with the new women to change things a little bit and so they believe that it agrees with Petersen, so that reflecting -- confirms if you want Petersen. They wouldn't have said that if they felt the data was just an entire replication of the same data, because they knew it wasn't quite.
Q. And the that that we're talking about Dr. Jewell is his quote from the Cornum paper in 2010, "Our data are from the same registers as those used by Petersen and colleagues, however, the study by Petersen and colleague was based on nationwide registries and included children born in Denmark between 1996 and 2003 right after that discussed the fact that there's a consistency there; correct?

A. Yes, and they were giving you those dates, because earlier in the paper they've given the dates they looked at and the counties that they looked at in Denmark which we've discussed actually this morning.

Q. And Dr. Jewell, you were just asked about this label, this proposed label and I want to quote from the label here. It says, "An increased risk of congenital cardiac defects, especially septal, the most common type of congenital heart defects was observed in some published epidemiological studies with first trimester Sertraline exposure." Is that wholly 110 percent consistent with your opinion?

A. Could you tell me the page number on that?

Q. I'm sorry, it's the label in the bottom right corner -- thank you, for this -- the bates number ends with 3746.

A. Okay. I'm there now. Sorry.

Q. You've got that and I'm sorry, it's in that first paragraph at the top --

A. Yes, I see -- right to the top of the page.

Q. Yes. Just after the Miles data that's put in there and it says, "An increased risk of congenital cardiac defects, especially septal, the most common type of congenital heart defects was observed in some published epidemiological studies with first trimester Sertraline exposure." That is wholly consistent with your opinion; is that correct?

A. That is correct. As I said to the other counsel, I

agree with that part of the sentence.
Q. And is it your appreciation having been across from Dr. Kimmel about the number of time said so far that he disagrees with that statement?
A. Well, I think you should ask Dr. Kimmel that question.
Q. Okay. And then they go onto talk about the confounding by the indication and underlying depression; correct?
A. And I commented on that that I think is an insufficient description of what actually happened.
Q. But that is something that you specifically in your report and ad nauseam over the past few days have discussed in great detail.
A. As I've said, my methodology demands a consideration of all kinds of bias, one which is confounding by indication.
Q. So methodologically those two, that one sentence is effectively consistent with the method you applied it's simply here. There's some concern about confounding by the underlying depression which you also share, so methodologically you went after that and it's unclear whether or not this even disagrees with your ultimate conclusion about that issue.
A. That is correct. I of course don't know the background analysis as was discussed that has been carried out by whoever proposed this language. It's clearly very briefly described their attention to confounding by indication, I would find it

hard to imagine that they methodologically did as advanced a look at the question as I did.

Q. But again, we don't know that?

A. But I don't know that. I don't, because I don't see --

Q. Dr. Jewell during your cross one of the issues that was brought up was the potential error in one of the slides.

A. Yes.

Q. In the upper bound of a confidence interval; do you recall that?

A. I do. Just before lunch.

Q. And have you -- did you examine that issue?

A. I did.

Q. And what was your conclusion?

A. The -- I actually need to see the one.

MR. ZONIES: May I approach, Your Honor?

THE COURT: Yes, you may.

THE WITNESS: Yes. Which slide because it was the other counsel who had these slides. Yes, okay. I've seen it now. This slide here which was the pie chart and is labeled Huybrechts-Jewell analysis has the correct odds ratio and the correct -- there it is that is correct. The upper bound is 3.3. Later on in the slides that with were used yesterday, that result was quoted again with an incorrect upper bound of the confidence and everything else was correct.

BY MR. ZONIES:

Q. Yes, and here's the same slide with -- in other words you've corrected it now with the 3.3. Is this the slide from yesterday?

A. Yes. That -- no, it's later on in these slides. That was already -- it's later on that was the second slide that counsel showed me. Yes, it's that slide that she's hold that where it's -- I think it says 1.9 where the, well, let's wait.

Q. Yes. This says 1.9, 1.1 to 3.3.

A. Well, that's the same, so --

Q. Right.

A. There was one that counsel showed me this morning that said 2. --

Q. That was this one that says 2. --

A. Oh, so it's been corrected now already? Yes, so this is the corrected version. Yes. So the 2.39 was transcription error of some form, so I gave away a little bit of my evidence inadvertently, by whoever transcribed the slide. So the correct confidence intervals is 1.1 to 3.3.

Q. And so would you prefer that this replace in deck?

A. Yes. This is the corrected version and that should be replaced.

MR. ZONIES: Your Honor, I don't know what we're going to do about this and I haven't discussed it with counsel, but we would ultimately would move for admission for record purposes at a minimum that the notebook that has the

studies in it and Dr. Jewell's report in it and the slide decks will provide the Court with colored version for the record as well.

THE COURT: All right. Is there any objection to any of the submissions by the PSE?

MS. YATES: No, objections, Your Honor. And we will provide the Court the same to the extent if you haven't already received it.

THE COURT: All right. Any objections to any of the defense exhibits?

MR. ZONIES: No, Your Honor.

THE COURT: All right.

MR. ZONIES: I mean, yes, to the exhibits, but --

THE COURT: They're all admitted anyway.

BY MR. ZONIES:

Q. One final line of questioning Dr. Jewell. Now, I'm not sure what the objection is, but there maybe some floating objection about your qualifications to reach the causal conclusion in this case. So, I'd like to explore those qualifications. Have you, Dr. Jewell, reached causal conclusions in other cases and/or in others settings?

A. Absolutely.

Q. Have you challenged on your qualifications and ability to do so and passed whatever that challenge was whether it was

Daubert or Frye or otherwise?
A. I certainly have survived those challenges whether it was about causation and I don't know, but I certainly survived them.
Q. And in some of those, Dr. Jewell, well, all of them, they were in areas about which you have limited exposure, for example in this very courtroom you testified about myocardial infarction; correct?
A. I did.
Q. And are you a cardiologist?
A. No.
Q. And in that case as well you've had to deal with the concept of myocardial ischemia as compared to myocardial infarction; do you remember that?
A. I did.
Q. And are you schooled enough to be able to give us a lecture on those issues?
A. No. I could only give you a lecture on how once the data has been -- the terms have been defined and applied to data how the data should be analyzed.
Q. And even in that case in Avandia in particular, if you recall myocardial ischemia was defined by the manufacturer and that was what was used; do you recall that?
A. That's correct.
Q. Right. You didn't make an independent cutting of the

data or do anything, you accepted those classifications by the experts?

A. I do, yes.

Q. Is that the same thing you kid here?

A. Absolutely the same.

Q. Have you published Dr. Jewell on causation and causation issues?

A. I have, yes, from a statistical perspective.

Q. And you mentioned a new book that you have coming out. What is the focus of that book?

A. Causation.

Q. What's the name of that book?

A. Causal Inference in Statistics a Primer.

Q. And have you published on the --

A. It's co-authored I should say. It's co-authored with Judea Pearl who's undoubtedly one of the world's leading experts on causation.

Q. And Dr. Jewell have you published on pregnancy before or are you in the future?

A. I have published papers before when I've been a statistician that have looked at pregnancy outcomes and the effect of chemical exposures, usually associated with pesticide exposure and pregnant women in California. And so are in the record in my CV and I currently have two papers in various stages of review on rheumatoid arthritis and during

pregnancy which actually uses the GEE model.
Q. Which you have also published on?
A. Yes.
Q. Oh, and speaking of that, there was a list of studies that were depression restricted studies that counsel discussed with you; do you recall that?
A. Yes.
Q. And that those somehow provide better evidence with which, I think you would agree?
A. I think it's very helpful as a first step to confounding my indication to do that.
Q. And counsel discussed with you Huybrechts, Bond, and Jimenez-Solem with their attempt to get at that too, did you recall that?
A. Yes.
Q. Counsel I don't think discussed with you Berard and the fact that that study is also depression restricted?
A. That is correct. The most recent -- her the, only one that I have, yes.
Q. That has that higher look at a smaller class trying to get rid of confounding; right?
A. By indication, yes.
Q. Right. Thank you, Dr. Jewell?
A. Thank you.
THE COURT: Any recross?

MS. YATES: Thank you. Two questions, Your Honor.

BY MS. YATES:

Q. Doctor, with regard to the Refuse study you seem to be critical of the fact that they used interviews in order to gather their data; right?

A. I'm not critical, that may have been the only data they had, but it's known to be less reliable as a measure of true exposure.

Q. And what method did the Cornum study use in obtaining their information?

A. I can't recall without going back to the papers. I know some of them by heart, but not that one to be explicit.

Q. Okay.

A. The registries in Denmark, certainly Jimenez-Solem used pharmacy records [indiscernible].

Q. I misspoke.

A. Oh, so you're not asking about Cornum?

Q. No.

A. Okay.

Q. Do you know what method Luick used?

A. Yes. Luick used I believe my memory is she used and her team used maternal interviews.

Q. Nothing further, thank you.

MR. ZONIES: Nothing further.

THE COURT: All right. Thank you. You may step down.

THE WITNESS: Thank you.

THE COURT: And we will adjourn for today and let's discuss the plan for tomorrow. Any other witnesses from the plaintiff.

MR. ZONIES: None, Your Honor.

THE COURT: Any other witnesses from the defendant?

MR. CHEFFO: No, Your Honor.

THE COURT: Then if the evidence is closed because we've admitted all of the charts and the documents and the binders and the additional documents then would you like to argue in the morning.

MR. CHEFFO: I think we would. We can do it relatively briefly and succinctly, but as Your Honor knows there's a lot of information the binders and things so obviously it's all for the Court and Your Honor's convenience and assistance, but we think it would be helpful to do within an hour or less of closing as we've done in the past and then to the extent after that if Your Honor would like any kind of post-hearing briefing, of course we would entertain that follow Your Honor's guidance on that.

THE COURT: I do not require post-hearing briefing, but I never like to deprive good counsel of their

last shot. Tomorrow one hour or less for each of you.

MR. CHEFFO: Okay.

THE COURT: We'll start and 10:00 and I would appreciate if we could really start on time and then get that done. And I are always find that that's helpful. The openings were helpful and the closing I trust will be just as helpful.

I'm not as impressed that briefing -- additional briefing is necessary, but I need to know how you both feel about that, Mr. Zonies?

MR. ZONIES: I don't, I wouldn't be impressed by my own brief either, so I think the Court has --

THE COURT: It's not personal, it's a blanket statement.

MR. ZONIES: I think the Court has a fine handle on the situation and I'm not [indiscernible] I might get a shot from somebody in the back.

THE COURT: You might.

UNKNOWN: I agree.

THE COURT: As he runs out of the courtroom.

MR. ZONIES: I don't think it, I certainly don't think it is necessary.

THE COURT: All right. Mr. Cheffo?

MR. CHEFFO: Again, I don't want to be one to force a brief on Your Honor, if you have a lot of paper --

THE COURT: Well, it's not that. The briefing was very, very complete in this matter.

MR. CHEFFO: Here's what I would say and then maybe we can talk to PSE on this. Again, I don't think we want to take a lot of time or a lot of pages and I'm not even sure we'll need it, so, may be I can call Chris with my folks and obviously we'll only do it if I think we can do something within a limited page limit that we think add to the story. If it doesn't then you don't need anymore and we don't need anymore.

THE COURT: Based on something that was surprising or came out that you don't feel each of you that you dealt enough with in the other briefs, I'll give you a chance to do that if you really need it.

As I said, I'm not going to preclude, but think about that overnight; all right?

MR. CHEFFO: Yes, thank you, Your Honor.

MR. ZONIES: And if I may clarify one thing, Your Honor, I understand that the evidence is technically closed and I happen to talk to Mr. Cheffo about this and I'm sure he'll let me know if this is a problem. Because we anticipated Dr. Kimmel was going to testify and because he is not testifying I've discussed with counsel that we would be permitted to use his prior testimony either through deposition or at the Frye hearing or elsewhere in our closing essentially

and argue that. And to the extent that that's not formally in evidence before the Court, when we argue that I would either, whatever counsel wants to do, move that in as additional evidence, it will be in the closing slides which we'll present to the Court as well.

THE COURT: Is that testimony at deposition or is it trial or is it Frye hearing?

MR. ZONIES: It is -- I'd have to see which ones I need to use, but I think it's Frye hearing.

THE COURT: All right.

MR. ZONIES: That was sort of the condition that which we didn't need call on.

MR. CHEFFO: This is what I would say, as a general matter that they obviously we didn't object to, I'm certain of the things they've -- I think they've referred to it in their brief. It's hard for me to say kind of blanket without seeing it we agree, but I think the rule of reason will apply and to the extent it's sworn testimony and we did say that to make things move a little quicker and not have to call Dr. Kimmel that we would understand that they'd be relying on certain prior testimony.

THE COURT: All right.

MR. CHEFFO: So, I guess generally yes, but we'll just want to reserve our rights depending on what he does.

THE COURT: Any record testimony could be relied on and it's not unfair surprise to anybody but me and it's not unfair, so I'll have a chance to read a transcript to bolster my understanding of whatever you're arguing about. So, that's fine with me.

MR. ZONIES: Thank you.

THE COURT: Work on that tonight. And is there anything else? Thank you very much.

MULTIPLE SPEAKERS: Thank you, Your Honor.

THE COURT: We're adjourned.

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(Whereupon, the proceeding was concluded at 5:10 p.m.)

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C E R T I F I C A T E

I do hereby certify that the aforesaid hearing was transcribed by me from an audio recording to the best of my ability; and that I am neither of counsel nor kin to any party in said action, nor interested in the outcome thereof.

WITNESS my hand and official seal this _____ day of _____, 2015.

Janine Thomas
Notary Public